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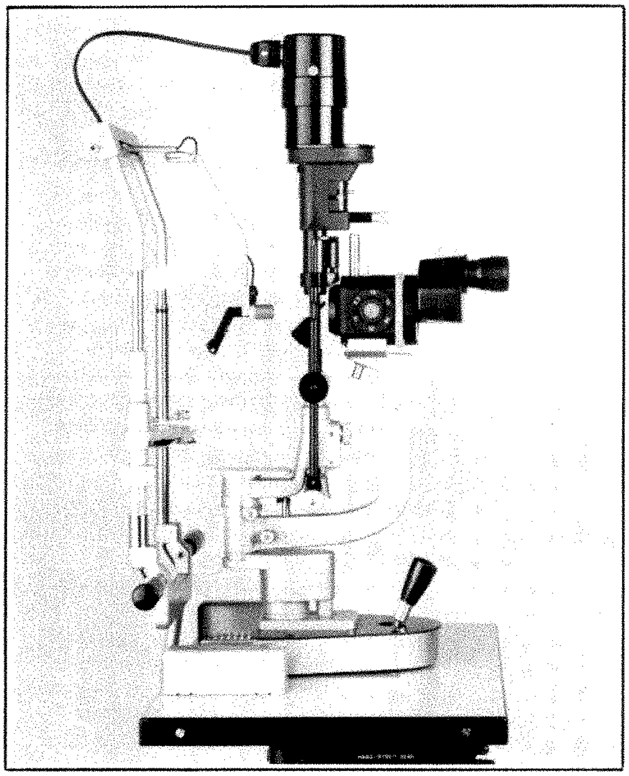

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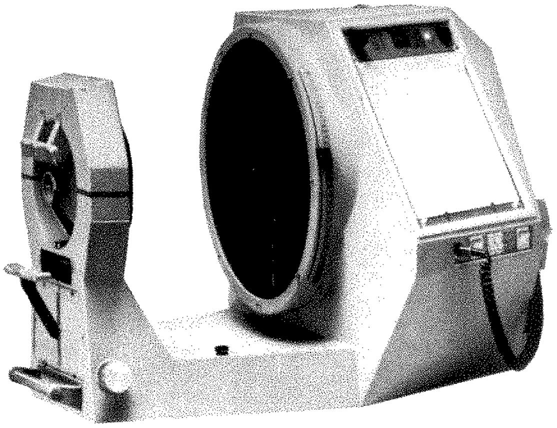

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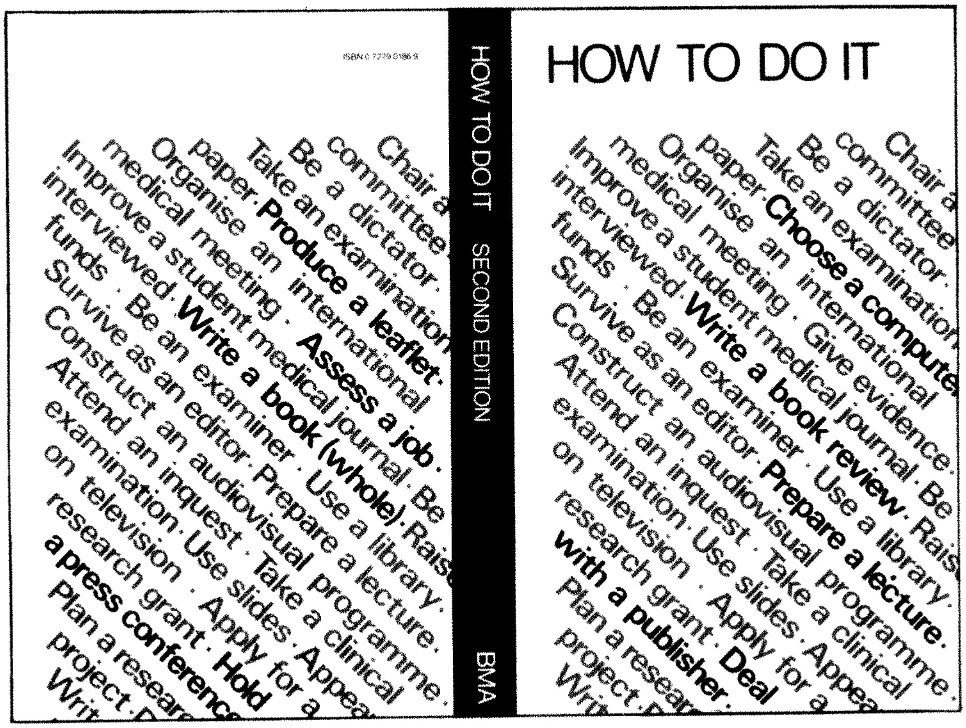

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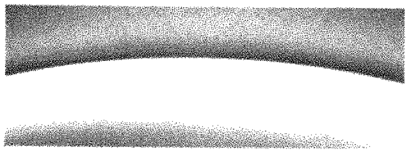

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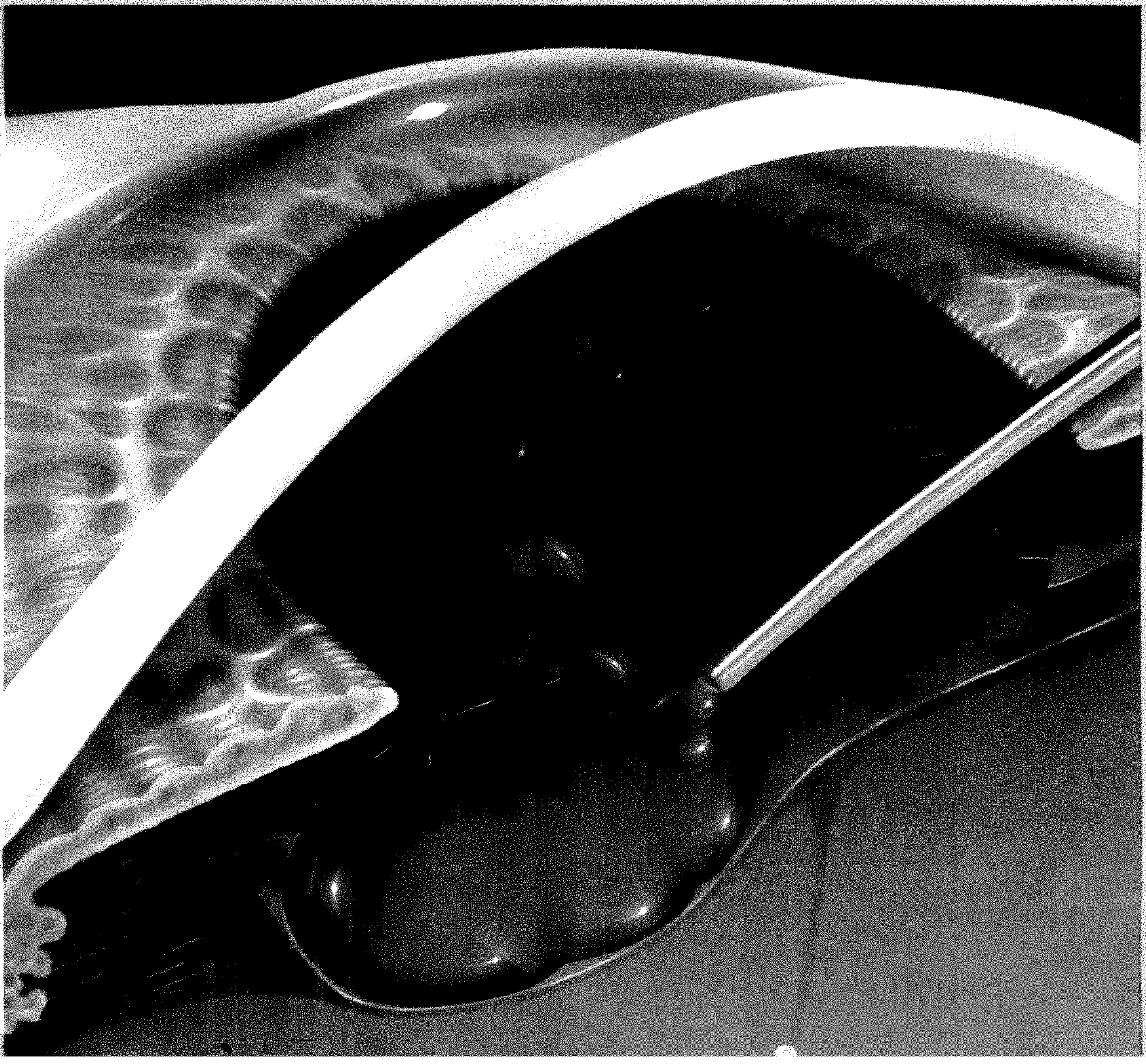

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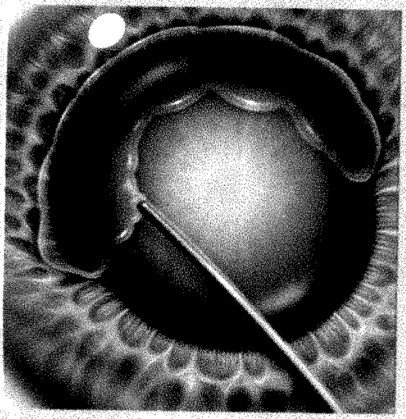

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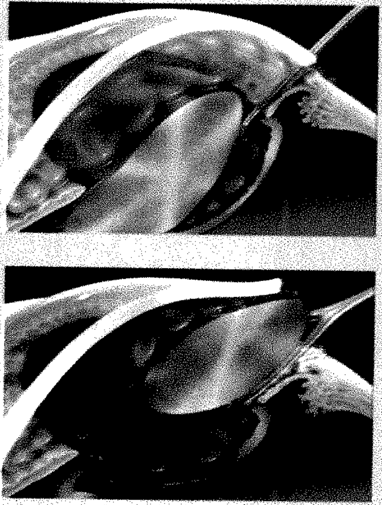

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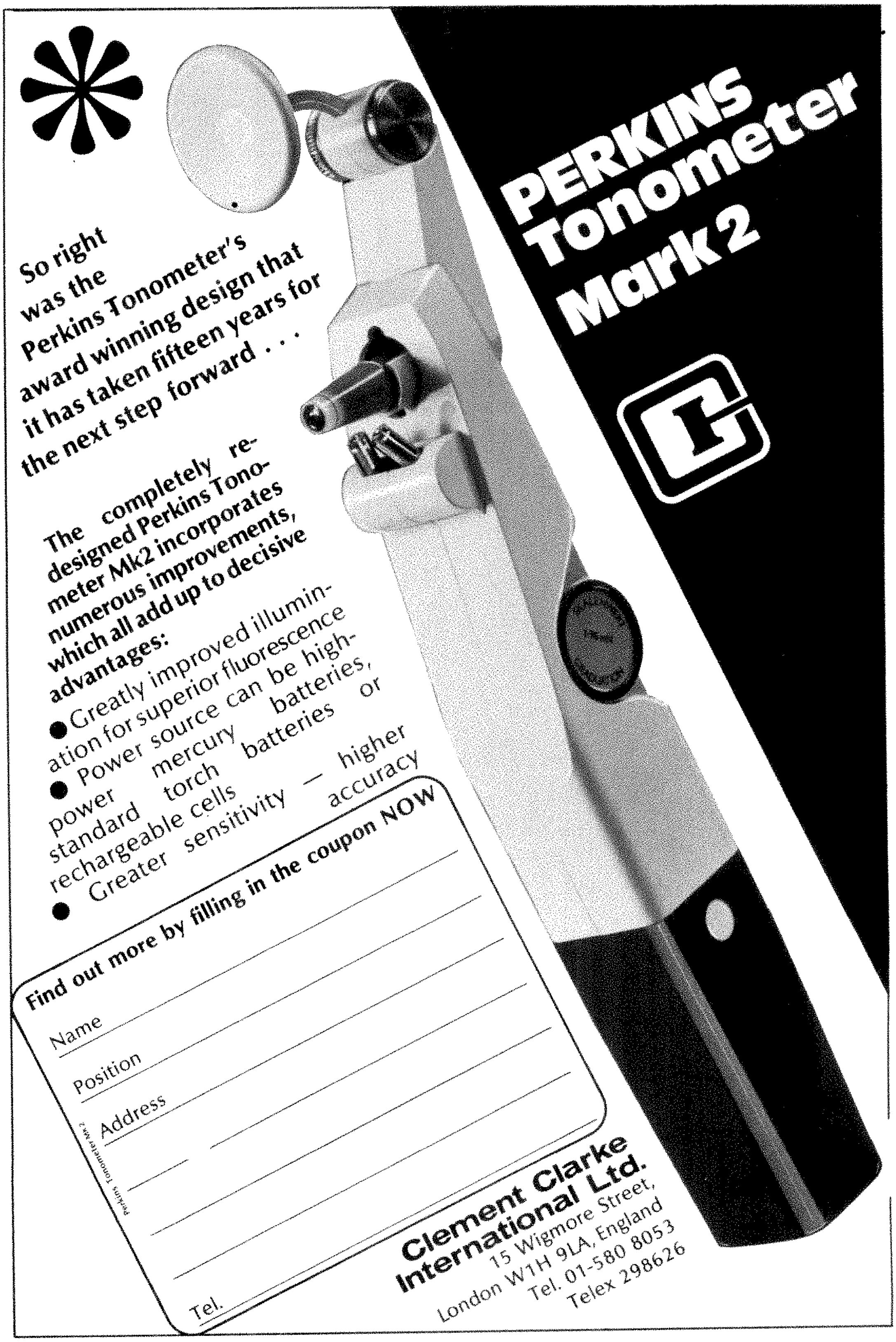

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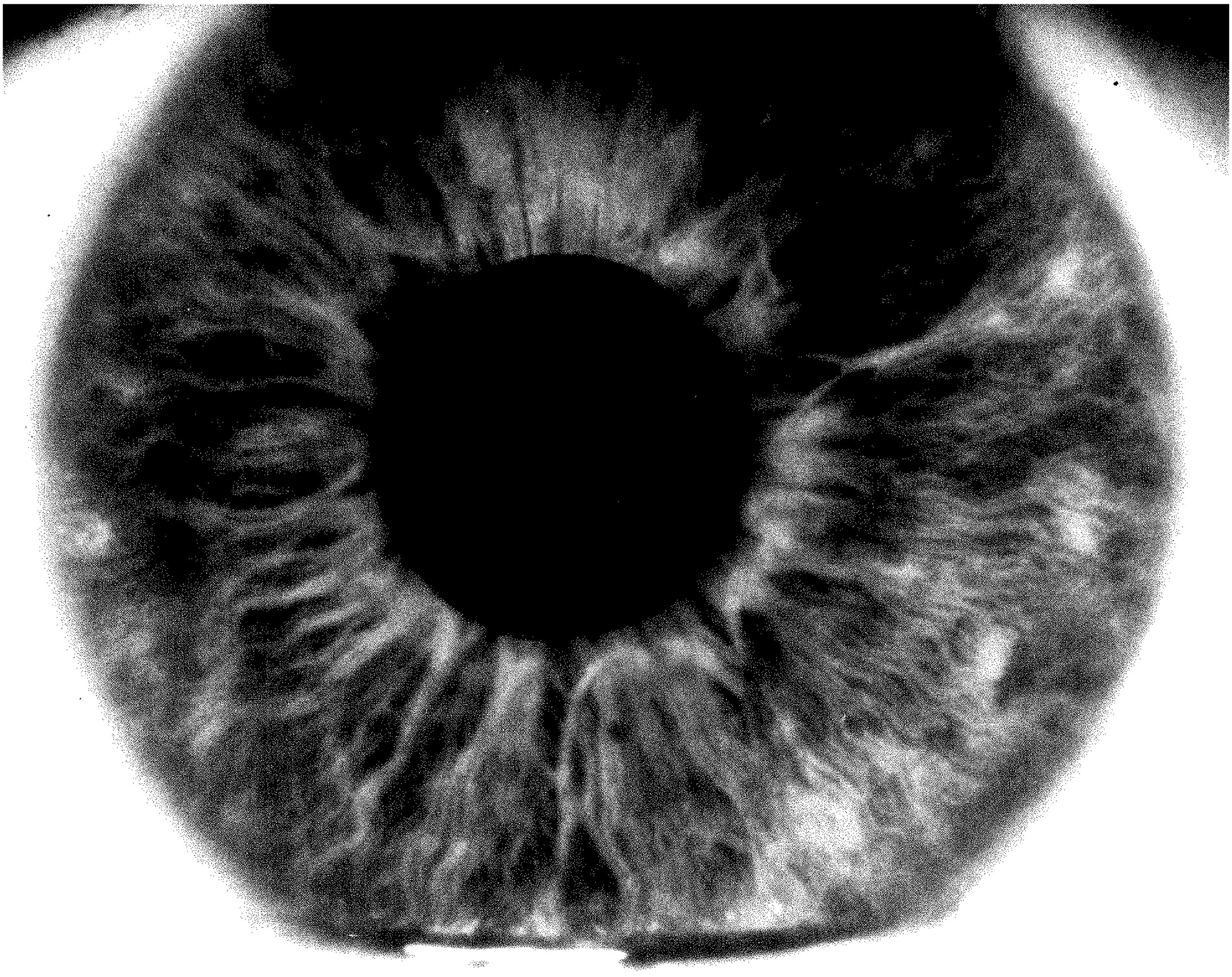

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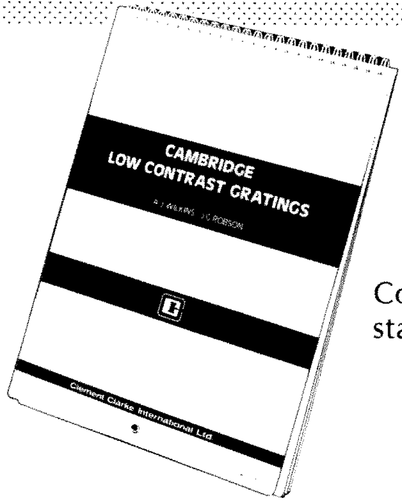

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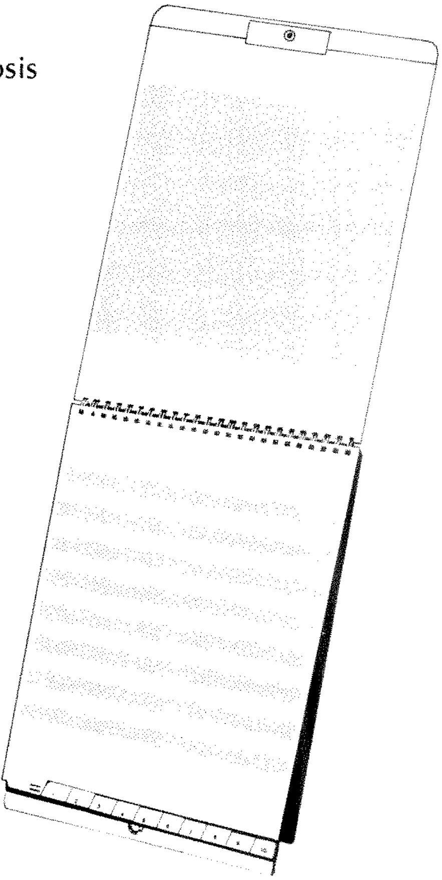

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Della Sala S, Somazzi L, Wilkins AJ. Rapid technique for detecting "blurred vision" in diseases of primary visual pathways. Lancet 1985; **2**: 1015-6.

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3. Lichter, P.R. et at., *Amer J Ophthalmol.*, 1978, **85,** (4), 495-502.

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British Journal of Ophthalmology, 1986, **70**, 481

Editorial: Jam tomorrow

Lasers are becoming increasingly useful in many branches of surgery and are already playing an important part in the control and management of various ophthalmic disorders. An interesting article from Professor John Marshall and his coworkers in this issue of the journal deals with some of the biophysical properties of the much talked about excimer laser. For most of us laser actions have been confined to those of photocoagulation and more recently photoablation, but the possibilities of what lasers may be able to do for surgeons are likely to be much more extensive.

This particular study makes a comparison between the quality of corneal incisions produced by currently used diamond and steel knives with two versions of incisions produced by an excimer laser. Traditionally, a physical cutting blade like a diamond or steel edge produces its cutting power by applying pressure to a very sharp edge and forcing the separation of tissue to which it is applied. Diamond is capable of being much sharper than steel because of the perfect edge which can be produced by virtue of its crystalline structure. Lasers, however, cut on an entirely different physical principle, and this article supports the hypothesis that the tissue is divided by the process of photomolecular decompensation. To the surgeon it is not yet clear whether the physical difference induced in the tissues by the different methods will affect the quality of wound healing. There certainly is much less tissue damage from incisions made by excimer lasers, and it may well be inferred that such incisions may be followed by a less vigorous healing process.

The paper is also interesting for those of us who have been using diamonds routinely for corneal surgery, for the study demonstrates neatly the improved quality of the incision produced and the reduction in the amount of tissue trauma. So far there has been no indication that incisions produced by a diamond end up with weaker scars than those produced by steel blades.

The only disadvantage which this particular study demonstrates is that deep laser made incisions in corneal stroma which do not quite perforate are associated with linear patterns of endothelial cell obliteration in the vicinity of the incision, a clearly undesirable feature. Despite this problem, which can almost certainly be modified, the excimer laser clearly has great surgical potential. Presumably it would not be difficult to engineer modes of making incisions in a variety of shapes – linear, curved, and circular – and we await the work needed to transfer what has been shown to be possible in the laboratory into instruments which can be used for clinical purposes. However, the expense will also have to be justified by significantly improved surgical results. Diamonds are not cheap, but they are certainly a great deal cheaper than the excimer laser is likely to prove.

What would be more interesting for us will be the application of an excimer laser not for the making of incisions but for the reshaping and moulding of surfaces, so that current techniques used for refractive surgery can be surpassed in terms of the speed of operation and accuracy of result. An excimer laser controlled by computer should be able to carve a corneal surface to any desired shape, eliminating in one step any undesirable refractive error except perhaps the irregular astigmatism of keratoconus, for which corneal grafting will probably continue to be the best final option. Those of us engaged in refractive surgery can therefore look forward to the arrival of such a tool with great pleasure. The obvious mechanical disadvantages for the eye, both optical and physical, resulting from radial keratotomy, keratomileusis, and epikeratophakia, will then happily be features of the past. Hopefully, so technical and unsurgical will these new refractive applications for the excimer laser be that they may be safely left in the hands of technicians, thereby freeing ophthalmic surgeons to get on with work to which they are more suited and for which their particular skills are in more demand.

ADMcGS

British Journal of Ophthalmology, 1986, **70**, 482–501

A comparative study of corneal incisions induced by diamond and steel knives and two ultraviolet radiations from an excimer laser

JOHN MARSHALL,[1] STEPHEN TROKEL,[2] STEPHEN ROTHERY,[1] AND RONALD R KRUEGER[2]

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SUMMARY This paper reviews the potential role of excimer lasers in corneal surgery. The morphology of incisions induced by two wavelengths of excimer laser radiation, 193 nm and 248 nm, are compared with the morphology of incisions produced by diamond and steel knives. Analysis suggests that ablation induced by excimer laser results from highly localised photochemical reactions and that 193 nm is the optimal wavelength for surgery. The only significant complication of laser surgery is loss of endothelial cells when incisions are within 40 µm of Descemet's membrane.

Excimer lasers may herald a new epoch in surgery of the cornea. The term excimer is derived from the first two and last syllables of the words that describe the physical state of the lasing media used in such lasers—*exci*ted di*mers* of inert gases. Excited dimers are two atoms of an inert gas bound in a highly excited state with atoms of halogen to form a temporary association as a diatomic rare gas halide. The decay of these unstable molecules is accompanied by the emission of a highly energetic photon of ultraviolet light. Excimer lasers are systems whose emission wavelengths are variable and determined by a specific energy transition, characteristic of the particular gases used to fill the lasing cavity. For example the emission for argon fluoride occurs at 193 nm, and that for krypton fluoride at 248 nm.[1] They emit their radiation as a train of individual pulses whose duration is typically about 10 nanoseconds, and with a pulse repetition frequency of between 5 and 15 Hz.

Interest in their surgical potential was initiated by reports from scientists in both the materials and electronic industries that the intense ultraviolet radiation emitted by such lasers could be used to etch submicron patterns into the surfaces of plastics and other polymers[2] with a remarkable degree of accuracy and with no degradation processes being conducted to unirradiated areas.[3,4]

The discrete focal localisation of the effects induced in target materials is currently under investigation. Two theories have been proposed. The first of these proposes that beam tissue interactions are predominantly the result of ultrafast thermal events, or so called photon-phonon interactions, and that the discrete nature of the induced change arises because of the very short penetration or adsorption depth of the ultraviolet radiation.[5] The second theory asserts that the target reaction is not thermal but probably photoablation, or photon-induced molecular decompensation.[6,7] The protagonists of photoablation suggest that molecules in the target area are released as a direct result of rupture of intermolecular bonds whose uncoupling is induced by absorption of high energy photons. Such a mechanism is possible, because in the ultraviolet spectrum individual photon energies are in excess of 6 electron volts and are thus capable of disrupting valency electrons. Thus only those molecules that absorb ultraviolet radiation directly are affected, and adjacent areas would show no conductive effects. It is suggested that, once molecules have been disrupted, the small, energetic, and volatile fragments rapidly ablate. This mode of action would produce the sharply defined boundaries of irradiated areas. It could also account for the smooth surface of the substrata exposed by surface erosion during excimer irradiation, with the total depth of the erosion being

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a function of the absorption depth at any given wavelength an the duration of the exposure.

The concept of photoablation with its implicit precision has provoked the initiation of a number of pilot studies involving irradiation of biological tissues.[8] Early results with high resolution troughs or trenches being eroded in such tissues as human hairs inspired Trokel to collaborate with Srinivasan and others to examine the potential of excimer lasers for corneal surgery.[9]

The present paper examines the erosions induced by two different wavelengths of ultraviolet light and attempts to consider the optimal factors for potential clinical use. In addition ultrastructural changes induced by lasers are compared with those generated by conventional instruments.

Methods and materials

LASER STUDIES

The laser used throughout the present study was a Model 102E Excimer laser produced by Lambda Physik (Gottingen, West Germany). The cavity was filled, to the manufacturers' recommended levels, with either argon and fluorine or krypton and fluorine gases in order to provide emissions at 193 nm or 248 nm respectively. Given both the practical problems and the expense of changing gases, experiments at the two different wavelengths were performed as a sequential series rather than consecutive individual exposures of alternating wavelengths. The laser was modified so that the cavity was configured as an unstable resonator, and this produced a marked decrease in the far field divergence of the emergent beam.

The laser output was shaped with a 15 mm quartz cylindrical lens and passed through a 15×3 mm aperture placed adjacent to the cylindrical lens. The convergent beam was focused directly on to the specimen target. At the focus the laser produced a sharp rectilinear image some 21 mm long. At 193 nm the total output of this laser was 80 mJ, but this was reduced to a maximum of 20 mJ after passing through the collimator and aperture. The output at 248 nm was significantly higher with values of up to 100 mJ and 50 mJ in comparable locations. The duration of individual pulses within the pulse train also varied with wavelength, being about 14 nanoseconds with argon fluoride and 9 ns in the case of krypton fluoride. One further variable is the rate at which the peak power is reached in any given pulse at the two different wavelengths.[1] There is a marked substructure in excimer laser pulses, and this may be of importance in analysing induced biological effects.

The laser was run at pulse repetition frequencies of either 3, 5, or 10 Hz and exposure durations were of 5, 8, 10, 15, 30, or 45 seconds. The higher frequencies and longer exposures were generally used at 193 nm, giving fluence or dose values of 150, 300, and 450 mJ/cm^2. These exposure parameters were derived from previous experiments where it was calculated that 1 J/cm^2 at 193 nm ablates corneal tissue to a depth of 1 μm.[9] It was hoped that this range of doses would provide specimens with a variety of depths of incisions, including full penetration of the cornea.

Fourteen albino rabbits each weighing about 2 kg were anaesthetised with intravenous phenobarbital. The animals were placed on a positioning board with the target eye held open with a lid speculum and the cornea centred at the focus of the laser delivery system. A vertical or horizontal incision was made on the cornea of each eye. The laser was imaged in such a way that the resultant incision extended over the limbus. Six of the animals were exposed to radiation at 193 nm and eight to 248 nm. All animals were killed between 5 and 30 minutes after exposure with an intravenous overdose of phenobarbital.

CONVENTIONAL INCISIONS

Four rabbits of similar size and weight were anaesthetised in an identical manner. Each eye was prepared and draped and one eye of each animal was incised by a steel blade and the other by a diamond knife. Two of the animals received incisions in the vertical plane and two received them in the horizontal meridian. All incisions were made by a single pass of the cutting instrument across the central cornea, and pentrating to between one-half and one-third of the corneal thickness. A new Sharpoint microsurgical blade was used for each of the steel knife incisions, and those of diamond were performed with a new trifaceted Micra diamond knife.

HISTOLOGY AND ULTRASTRUCTURE

Immediately after death the eyes were removed, and a 5 mm penetrating incision was made at the ora serrata before the globes were placed in 3% glutaraldehyde buffered in Earl's buffer at 4°C. After 24 hours in this initial fixative the eyes were examined under a dissecting microscope, and corneal samples were isolated and divided such that each site of irradiation or conventional incision could be processed for examination by both scanning (SEM) and transmission (TEM) electron microscopy.

Specimens for SEM were postfixed overnight in 2% osmium tetroxide buffered in 0·1 M sodium cacodylate. They were dehydrated through a series of ascending concentrations of acetone in water before being critical-point dried (Emscope CPD 750). Dried samples were coated with a 30 nm layer of gold in a sputter coater (Emscope SC 500) prior to being examined in either a Hitachi 510 or 520 scanning electron microscope.

For TEM, specimens were postfixed for only 1 hour in the osmium tetroxide solution described above, dehydrated in alcohol, and then embedded in Araldite (CY212) via epoxypropane. Sections were cut at 1 μm on glass knives for light microscopy (LM) and on diamond knives in a Reinchert OMU4 ultramicrotome for electron microscopy. Sections were mounted on 200 mesh copper grids, and stained with uranyl acetate and lead citrate before being examined in an AE1 801 transmission electron microscope.

Results

As anticipated, the range of exposure parameters used in the laser studies resulted in a variety of depths of erosions with several through-and-through incisions at each of the two wavelengths. The most striking feature of laser induced incisions was the focal definition and the rigidly parallel nature of the smooth edges of troughs ablated by argon fluoride emissions at 193 nm (Fig. 1a). These were in stark contrast to erosions induced by the krypton fluoride emissions, where, although the boundaries were smooth, adjacent tissue damage was irregular and diffuse (Fig. 1b), as were those of incisions produced by both diamond (Fig. 1c) and steel knives (Fig. 1d). All wounds in the corneal stroma regardless of mode of induction resulted in a marked swelling with stromal thickness increased by up to one-third when compared with adjacent areas (Fig. 1).

The appearance of non-penetrating incisions was directly related to their mode of induction. Where argon fluoride emissions fell normal to the corneal surface, flat bottom troughs of varying depth were eroded (Fig. 2a). However, when the radiation struck the cornea obliquely, V-shaped grooves were apparent. Erosions by krypton fluoride were characterised by a zone of debris which had a peculiarly smooth surface (Fig. 2b). This debris covered the entire area of irradiation in superficial wounds, or both edges of the wound in cases of deep ablation. In appearance the smooth surfaced zone looked analogous to a condensed or solidified mass of previously molten material like metal running from a smelting furnace or lava from a volcano. Diamond knife incisions were seen as fine linear slits whose edges were closely appositioned (Fig. 2c), while those created by steel were V-shaped with gaping and irregular margins (Fig. 2d).

In all penetrating incisions induced by either wavelength of the laser the total ablation of intervening tissue resulted in the complete occlusion of the incision as the two walls collapsed and came to lie in anatomical juxtaposition.

THE EPITHELIUM

SEM preparations demonstrated one of the practical limitations of the crude delivery system used for the laser studies—that of presenting a repetitively pulsed exposure of several seconds' duration to a target capable of involuntary movement. In several experiments eye movements had occurred during the laser exposure and resulted in consecutive pulses falling on different target locations. Such specimens showed a series of parallel superficial excorations where varying numbers of epithelial cells had been debrided. The surface topography of these grooves differed with wavelength of the causal radiation, while the depth varied with the effective exposure duration, that is, the number of laser pulses falling on any given area.

Argon fluoride laser irradiation (193 nm)

At this wavelength all areas of ablation showed epithelial damage with the respective edges of the wound having curved margins such that, when they were measured at right angles to the axis of the incision, the width of the damage in the surface cell layer was always greater than that in the layer of basal cells (Fig. 3a). These curved margins were considered to have arisen through the release of elastic tension within the surface layers of the epithelium.

On SEM, surface cells adjacent to the margins of the trough had irregular boundaries, but the damage zone was confined within the dimensions of a single surface cell on each border.

Fig. 1 *Light micrographs of rabbit corneas incised by* (a) *an argon fluoride excimer lasr (193 nm);* (b) *a krypton fluoride excimer laser (248 nm);* (c) *a Micra diamond knife;* (d) *a Sharpoint steel blade. The bar markers are 100 μm.*

Fig. 2 *Scanning electron micrographs of the epithelial surface of rabbit corneas incised by* (a) *an argon fluoride laser (193 nm);* (b) *a krypton fluoride laser (248 nm);* (c) *a Micra diamond knife;* (d) *a Sharpoint steel blade. In contrast to conventional incisions, in both laser induced kerfs the ablated surface is smooth. The broken cells in* (a) *(arrowed) are an artefact of preparation, and the red blood cells within the cleft came from severed limbal vessels. The bar markers are* (a) (b) (d) *50 μm and* (c) *20 μm.*

Fig. 3 *Light* (a, c) *and electron* (b, d) *micrographs of incisions induced in the rabbit cornea by an argon fluoride excimer laser. The incised surface is extremely regular and bounded by a dense condensation or pseudomembrane (arrowed), which is particularly apparent in the stroma* (c, d). *The bar markers are* (a) *50 μm,* (b) *100 μm,* (c) *20 μm, and* (d) *1 μm.*

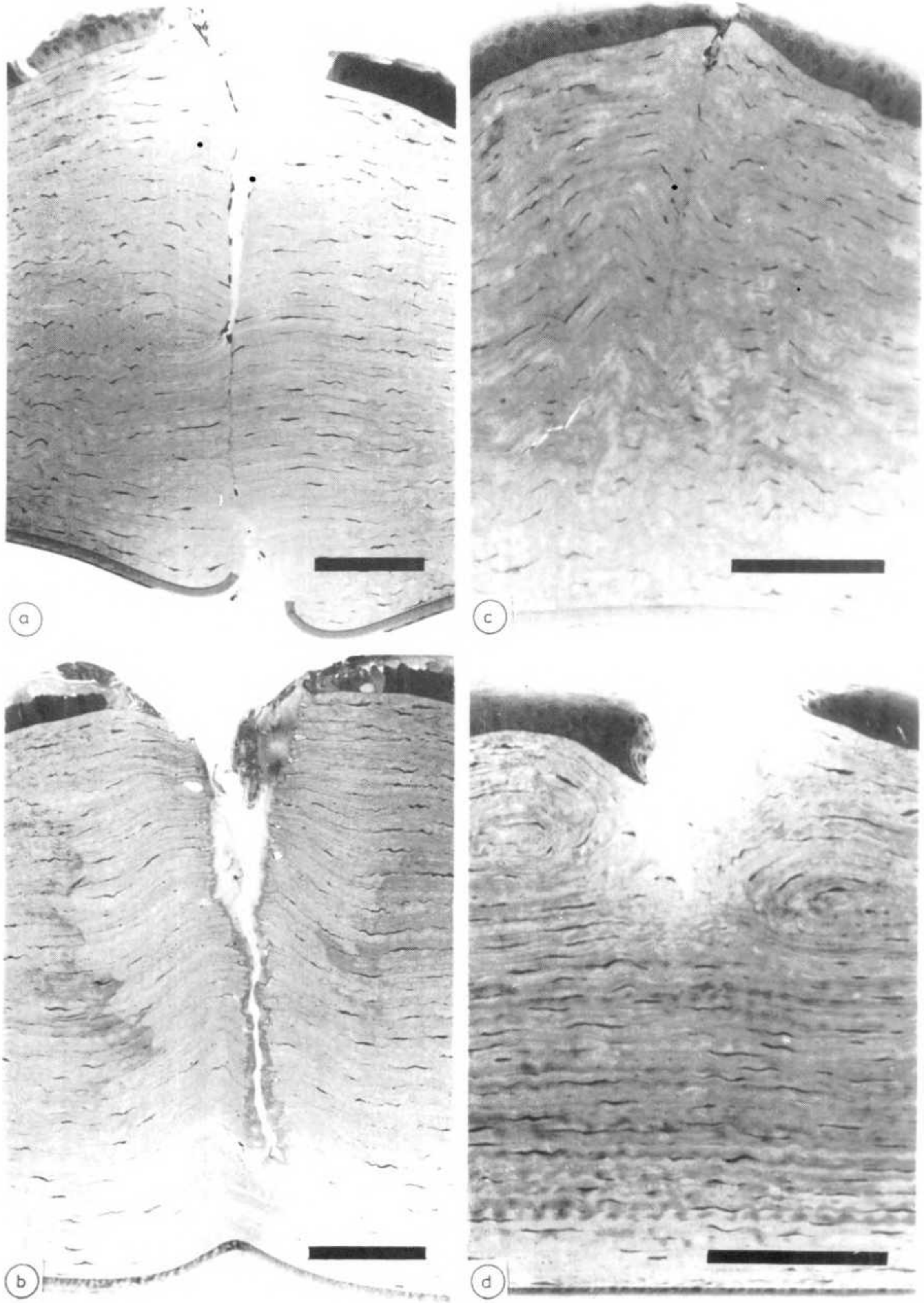

Fig. 1

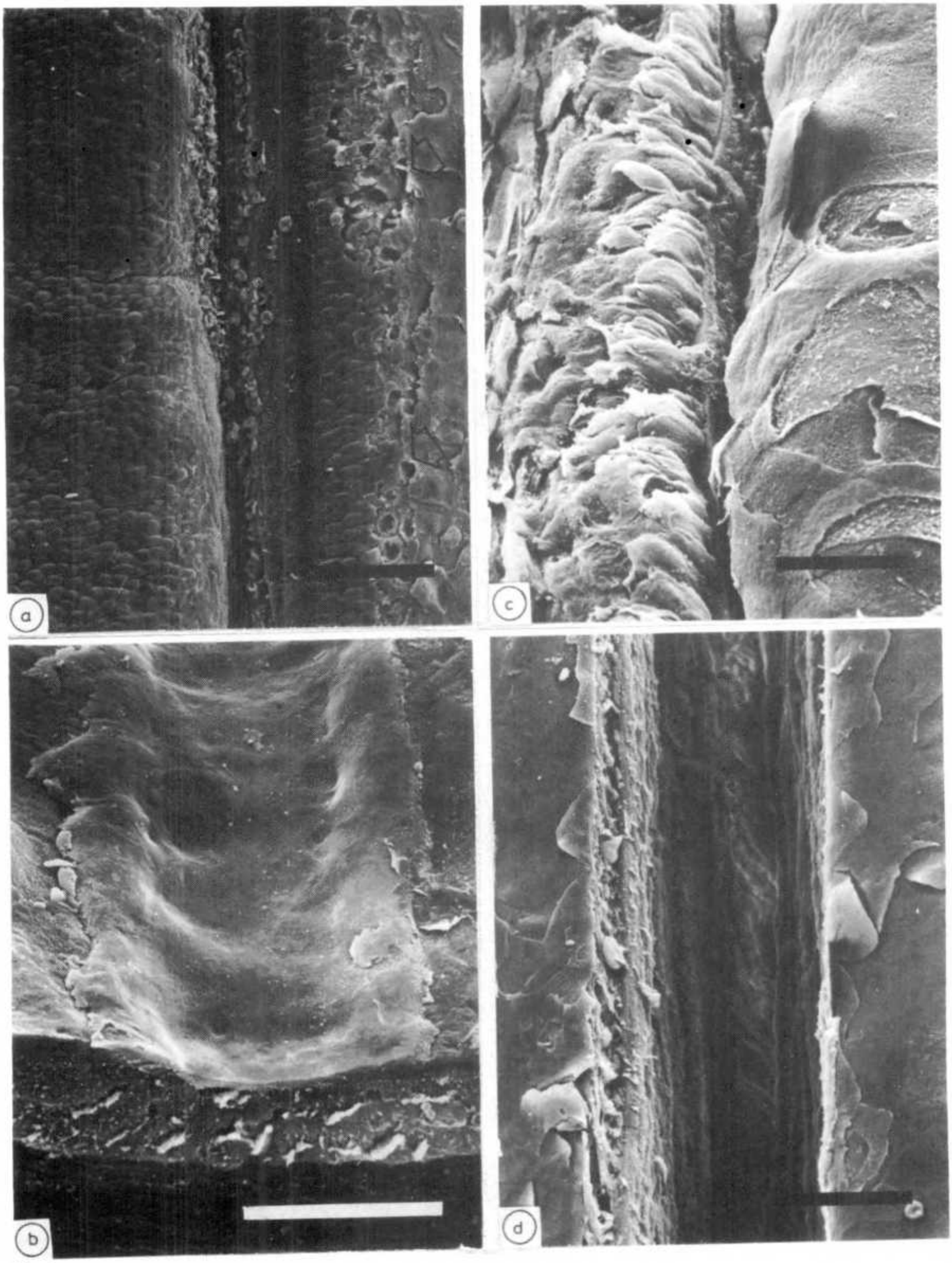

Fig. 2

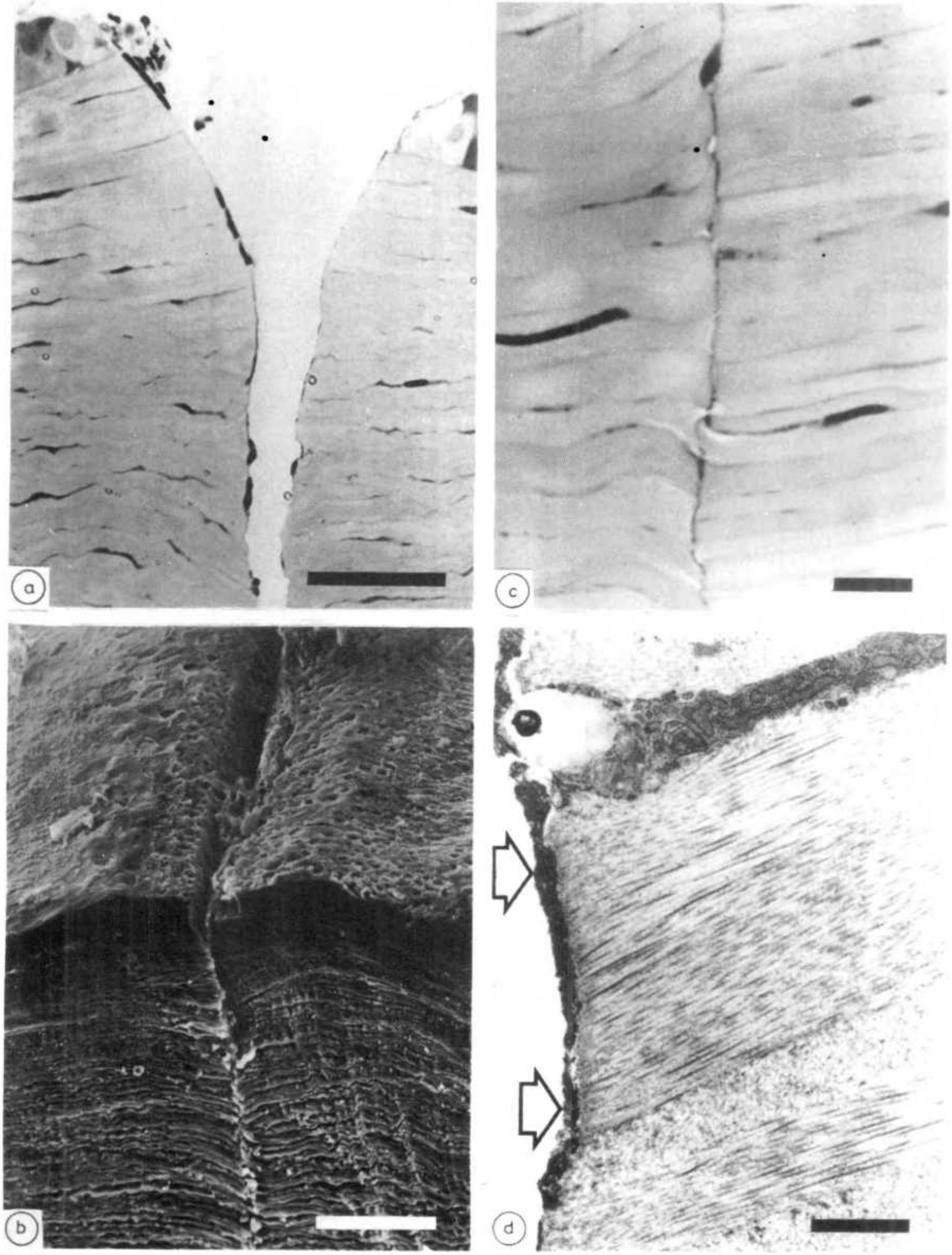

Fig. 3

In LM sections the epithelial aspect of the ablated areas always had curved clean edges, with the cells nearest to the incision showing no demonstrable effects of damage other than staining slightly less densely than their immediate neighbours (Fig. 3). The interface between these cells and the ablated tissues seemed at this level of magnification to be a conventional cell membrane. This was deceptive, as TEM specimens demonstrated that the pale staining cells had no cell membrane on their aspect in apposition to the irradiated area (Fig. 4). These cells had literally been cleaved by the ablation process. The severed edge was bounded by an electron dense condensation, which had little substructure and was seldom greater than 100 nm in thickness. Given such an unphysiological set of boundary conditions it is difficult to discuss this zone in terms of intra- and extracellular components, but in general the most superficial or 'extracellular' component was highly electron dense, while the slight condensation on the cellular aspect of the boundary was less so. This condensed pseudoborder of cleaved cells seemed to convey some sort of integrity to the cell remnants, as organelles and background cytoplasm appeared relatively normal other than being atypically electron translucent. In all incisions a discontinuous distribution of relatively homogeneous staining debris was found on the epithelial surface at both margins. The only discernible substructure present in this amorphous mass was a series of ribbons of electron dense pseudomembranes like those described above.

Krypton fluoride laser irradiation (248 nm)

The epithelial surface of areas adjacent to zones of krypton fluoride ablation was always covered by a smooth mass of tissue apparently congealed from a fused or fluid state (Fig. 5). The distal margin of this 'lava zone' was highly irregular, undulating like the margin of a wavelet dissipating itself on a beach (Fig. 5b, c). The proximal margin became more irregular the deeper the ablation penetrated the epithelium, and within the basal layer it usually displayed a pitted or broken surface.

In LM sections superficial erosions appeared as smooth surfaced grooves, apparently caused by compression of the surface layer of cells. Just beneath the surface of grooves cells were pale staining. In contrast, where incisions had penetrated the epithelial layer, the surfaces of the wound edges were densely staining.

TEM examination demonstrated that in superficial ablations the smooth surface of the troughs was a thin crust (3 to 4·5 μm) of medium electron density which appeared to consist of the compacted and denatured elements of the irradiated cells (Fig. 4b). The ablation surface was perfectly smooth and featureless and was not a cellular membrane system. The pale staining cells observed with the light microscope were seen to extend over one or two cell layers (8 to 13 μm) and consisted of vacuolated cell ghosts which had lost all their organelles, but whose erstwhile boundaries were delineated by vestiges of the desmosomal system. Beneath the pale zone the deeper cells were abnormally electron dense, and in many cases these cells had pyknotic nuclei and displayed swollen intercellular spaces between desmosomal junctions.

In incisions that had penetrated the epithelial layer the wash of congealed 'lava' appeared as a stratified mass of alternating high and low electron density (Fig. 5d). The denser of these two components looked like a highly convoluted sheet of coagulated cell debris, but was far coarser in substructure than the homogeneous ribbons of pseudomembranes seen in areas of argon fluoride irradiation. The pale strata were merely the spaces between sheets, but had acquired an apparent textural organisation because of the aggregation of flocculent material breaking off from the edges of the dense laminae. Close to the margins of these wounds the debris was opposed to vacuolated cell ghosts similar in distribution and morphology to those seen in superficial ablations. At the distal border of the 'lava zone' debris coated the surface of normal cells.

Conventional incisions

In contrast to laser induced ablations, which are essentially a no-touch technique, with conventional

Fig. 4 *Transmission electron micrographs of rabbit corneal epithelial cells incised by* (a) *an argon fluoride excimer laser;* (b) *a krypton fluoride excimer laser;* (c) *a Micra diamond knife; and* (d) *a Sharpoint steel blade. The pseudomembrane (arrowed) bounding the incised cells in* (a) *seems to contain the cell contents within cleaved cell fragments. This is in contrast to cells incised with either of the conventional cutting devices, where contents are evulsed from the cleaved surfaces* (c) (d). *In superficial damage induced by the krypton fluoride laser* (b) *a compacted surface layer is apparent (arrowed) overlying a zone of vacuolated cells. The bar markers are* (a), (b), (d) *5 μm and* (c) *2 μm.*

Fig. 5 *Scanning* (a) (b) (c) *and transmission* (d) *electron micrographs of rabbit corneal epithelial cells ablated by a krypton fluoride excimer laser. The problems of eye movements ar seen in* (a), *where a deep (open arrow) and superficial (closed arrow) pair of parallel incisions occur as a result of target movement during the pulse train of the laser exposure. The lava-like smooth surfaced debris (arrowed) is shown in* (b) *and* (c) *and its lamina substructure is demonstrated in* (d). *The bar markers* are (a) (b) *100 μm,* (c) *50 μm and* (d) *2 μm.*

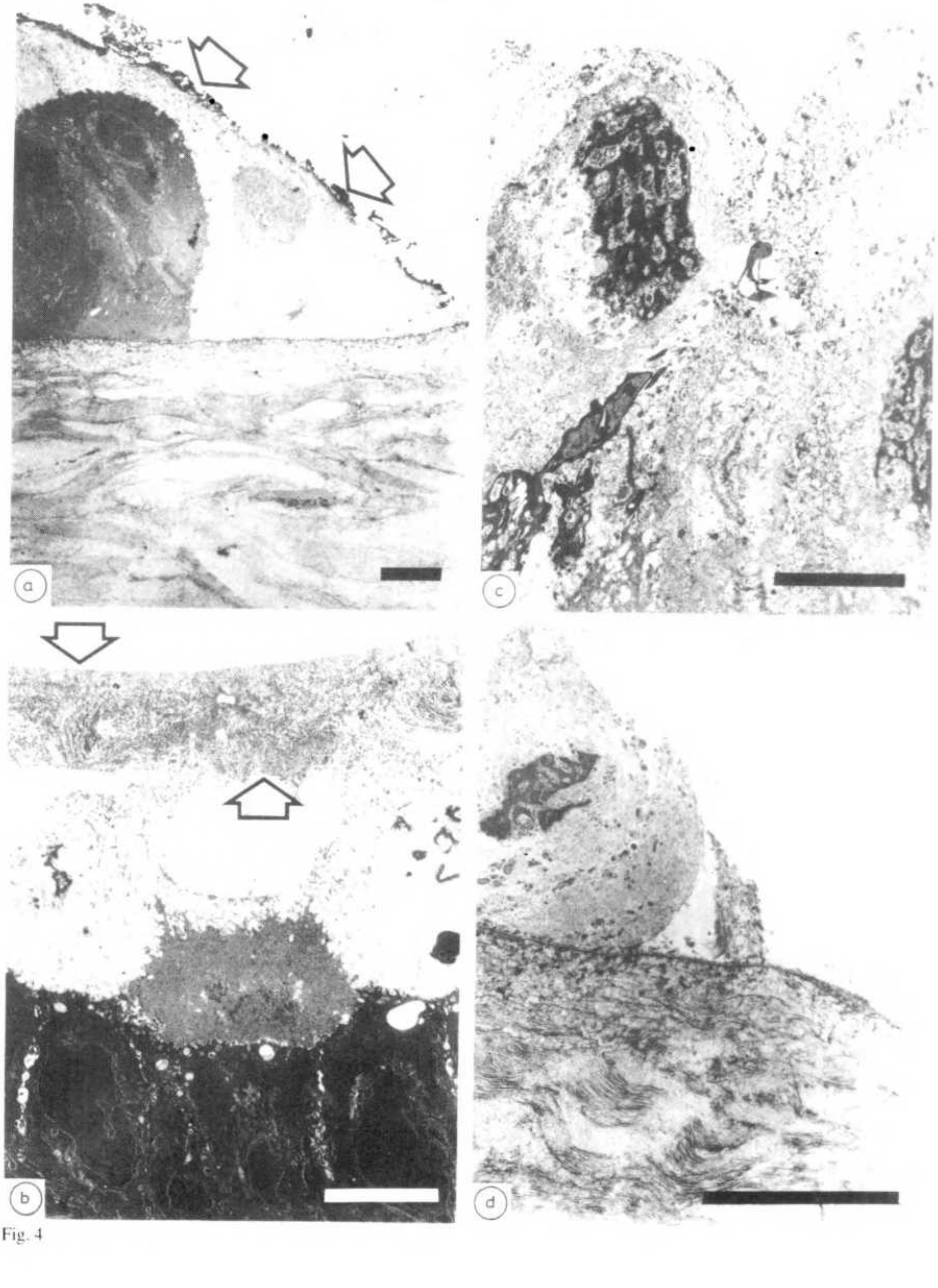

Fig. 4

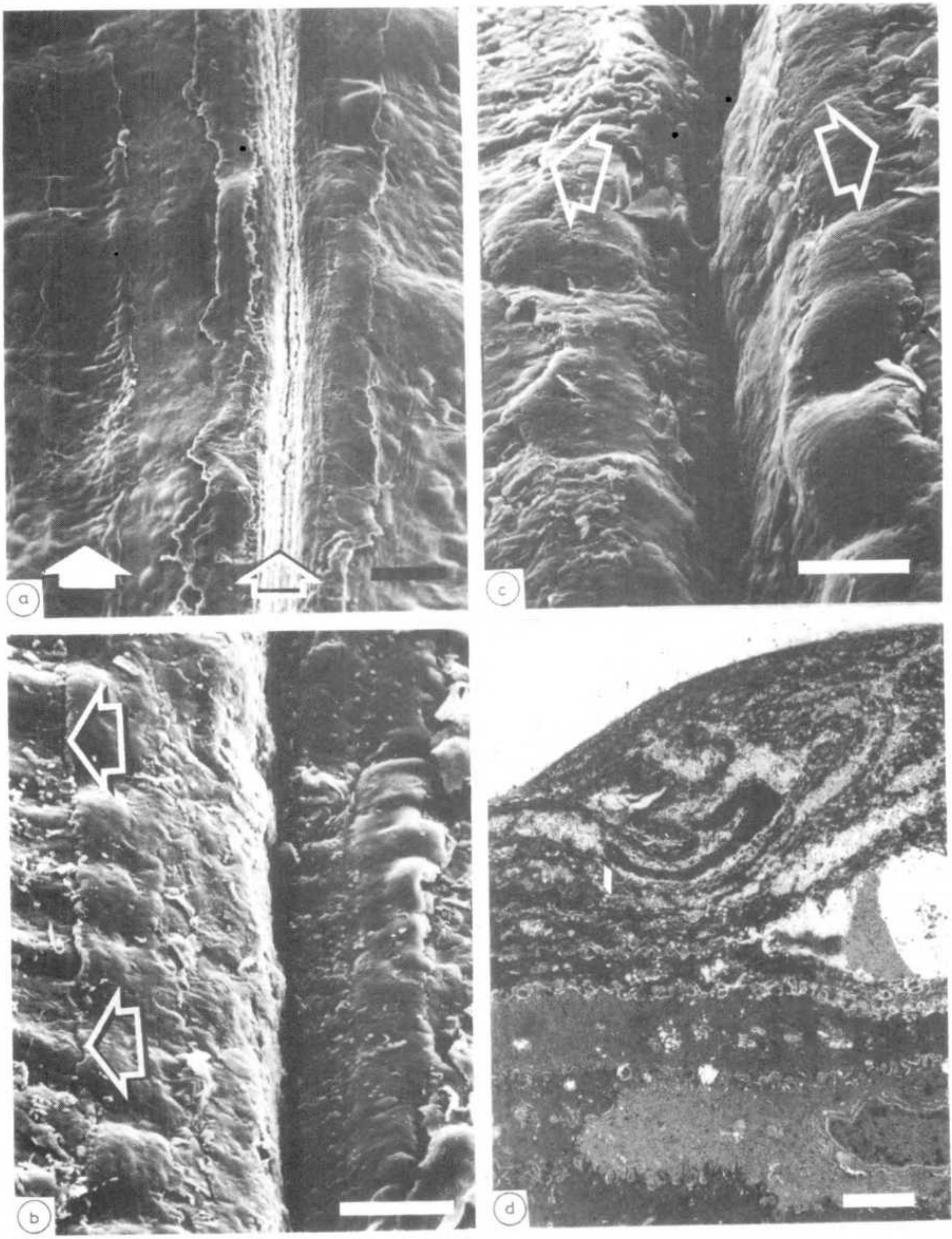

Fig. 5

surgery there is a degree of tactile feedback resulting from tissue drag as the cutting instrument is moved. The drag factor was noticeably higher with steel blades than with diamond knives, and eyes cut with the former required a greater degree of counter traction or fixation during cutting.

Diamond. Incisions produced by the Micra knife caused virtually no traction distortion to the surface cells of the epithelium (Fig. 6). SEM showed that the borders of such incisions either were lined by the virtually undisturbed but hemisected components of surface cells, or were bounded by normal epithelial cells that had migrated over the lip of the microcrevasse induced by the passage of the instrument (Fig. 6b, c).

In TEM preparations all diamond knife incisions were confined to within one cell diameter in width. Usually in such preparations a slight furrow was seen in the epithelial surface, and beneath this epithelial cells were displaced towards the stroma (Fig. 6d). In some incisions epithelial cell debris was displaced to lie within the confines of the incision in this deeper layer.

Steel. Incisions induced by the Sharpoint microsurgical steel blade were always much wider than those induced by the diamond and were usually 20 µm to 65 µm in width at the corneal surface (Fig. 7). Although these particular blades are ground on both aspects, the resultant wounds tended to be asymetric V-shaped troughs whose most angular wall corresponded to the laterality or handedness of the surgeon (Fig. 7a, b).

The role of tissue resistance in relation to cuts produced by steel blades was clearly demonstrated in SEM preparations where angular folds or microstress lines were seen distorting the surface cells for some distance on either side of the wound (Fig. 7c). The angles at which the stress lines ran in relation to any given incision varied with the depth of the incision, the magnitude of the applied pressure, and the speed of traverse of the blade through the tissue. In general, increase in any or all of these factors resulted both in an increasing frequency of folds and in the acuteness of the angle they made with the line of the incision.

Sections through wounds induced by steel blades showed significant damage on both margins, with epithelial cells being disrupted and torn (Fig. 7d). Cleaved cells immediately adjacent to the incision displayed a diffuse zone of subcellular debris avulsed from the torn surface. In many instances the basal cells bordering the cleft were dislodged from their basal membrane and compressed both upwards and outwards from the line of the incision. This compression or contusion injury extended to some four or five cells in width on both aspects of the cut surfaces.

THE STROMA

Argon fluoride laser irradiation (193 nm)

SEM preparations demonstrated the preservation of the focal nature of the ablative process even at the deepest layers of the stroma some 250 µm from the epithelial surface. All incisions resulted in an overall swelling of the stroma, although the degree of separation between individual lamellae in some SEM preparations was probably an artefact associated with the critical-point drying process. In penetrating incisions the marginal portions of the most superficial lamellae on both the internal and external aspects of the stroma converged to round off the respective borders of the ablated areas.

In LM and TEM the pseudomembranes seen bounding the ablated edges of epithelial cells were again present and in this location appeared as densely staining lines bordering the irradiated areas and running across the axis of the stromal lamellae (Fig. 3c, d). In penetrating incisions where collapse of the trough had resulted in juxtaposition of the respective edges this pseudomembrane zone became as narrow as 150–300 nm in width (Fig. 8a). As in the epithelium, this zone had two components with a highly electron dense surface condensation 20–100 nm, and a less dense intralamellar portion 60–200 nm. The intralamellar condensation seemed to be predominantly associated with changes located within the glycoprotein matrix of the lamellae as changes in the staining properties of lamellar collagen was rarely observed. In some few cases individual collagen fibres were observed to have passed out of lamellae and to lie axially within the incision. In those exposures that involved the incision of conjunctival blood vessels blood products, including red and white cells and fibrin, were observed in association with the edges of the troughs throughout their corneal portions. The presence of these blood components to some extent complicated the analysis of changes observed in the border zones, and made it

Fig. 6 *Light* (a) *and electron* (b) (c) (d) *micrographs of incisions in the epithelial cells of a rabbit cornea, created by a Micra diamond knife. The path of the incision in the transmission electron micrograph* (d) *is arrowed. The bar markers are* (a) (b) *50* µ*m,* (c) *10* µ*m and* (d) *2·5* µ*m.*

Fig. 7 *Light* (a) *and electron* (b) (c) (d) *micrographs of incisions in the epithelial cells of a rabbit cornea, induced by a Sharpoint steel blade. The asymmetry of the kerfs produced by this treatment is seen in* (a) *and* (b) *and showed the laterality of the surgeon. The stress lines induced in tissue by even new steel blades can be seen (arrowed) in* (c). *The bar markers are* (a) (b) *50* µ*m,* (c) *10* µ*m, and* (d) *1* µ*m.*

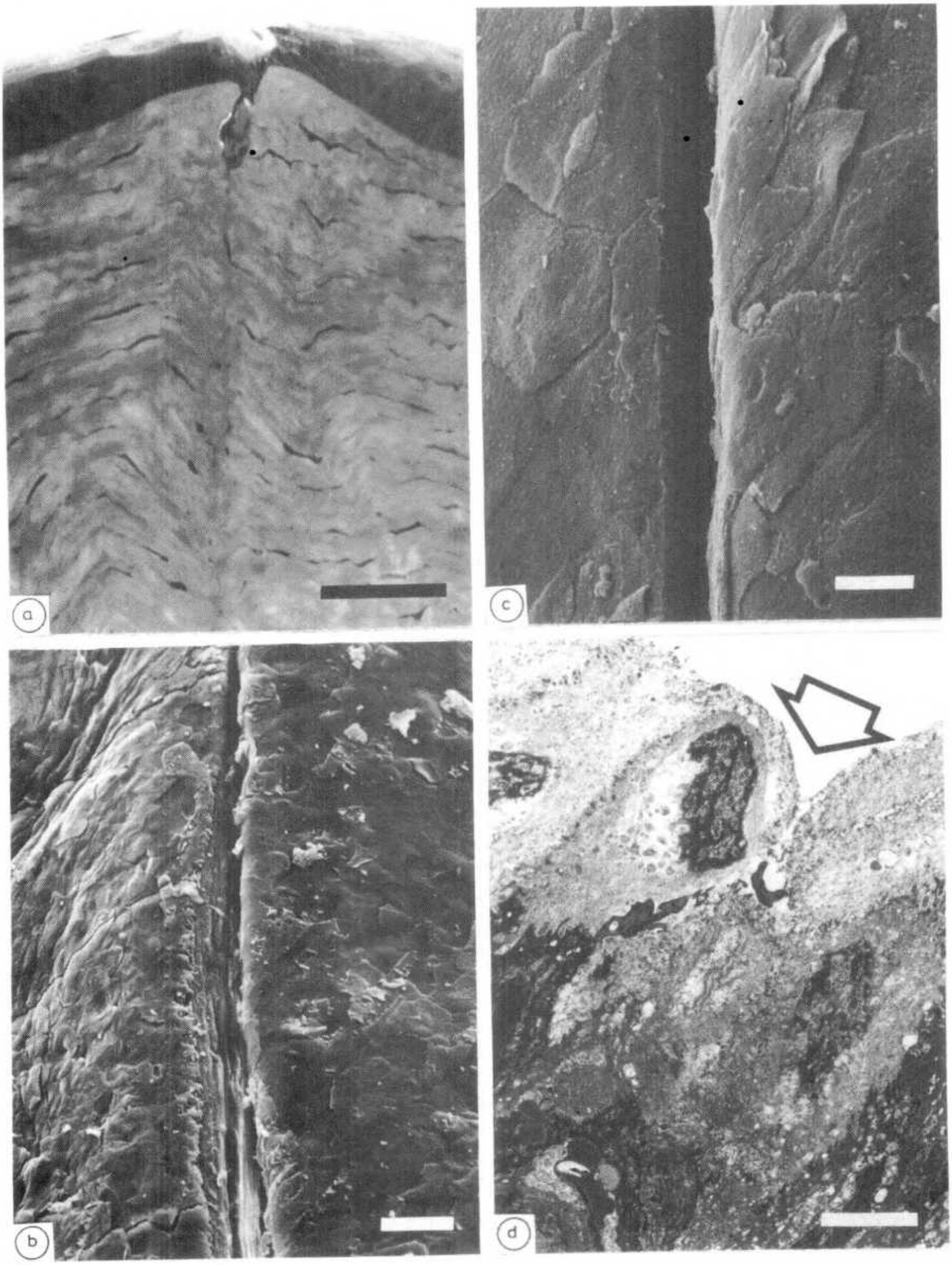

Fig. 6

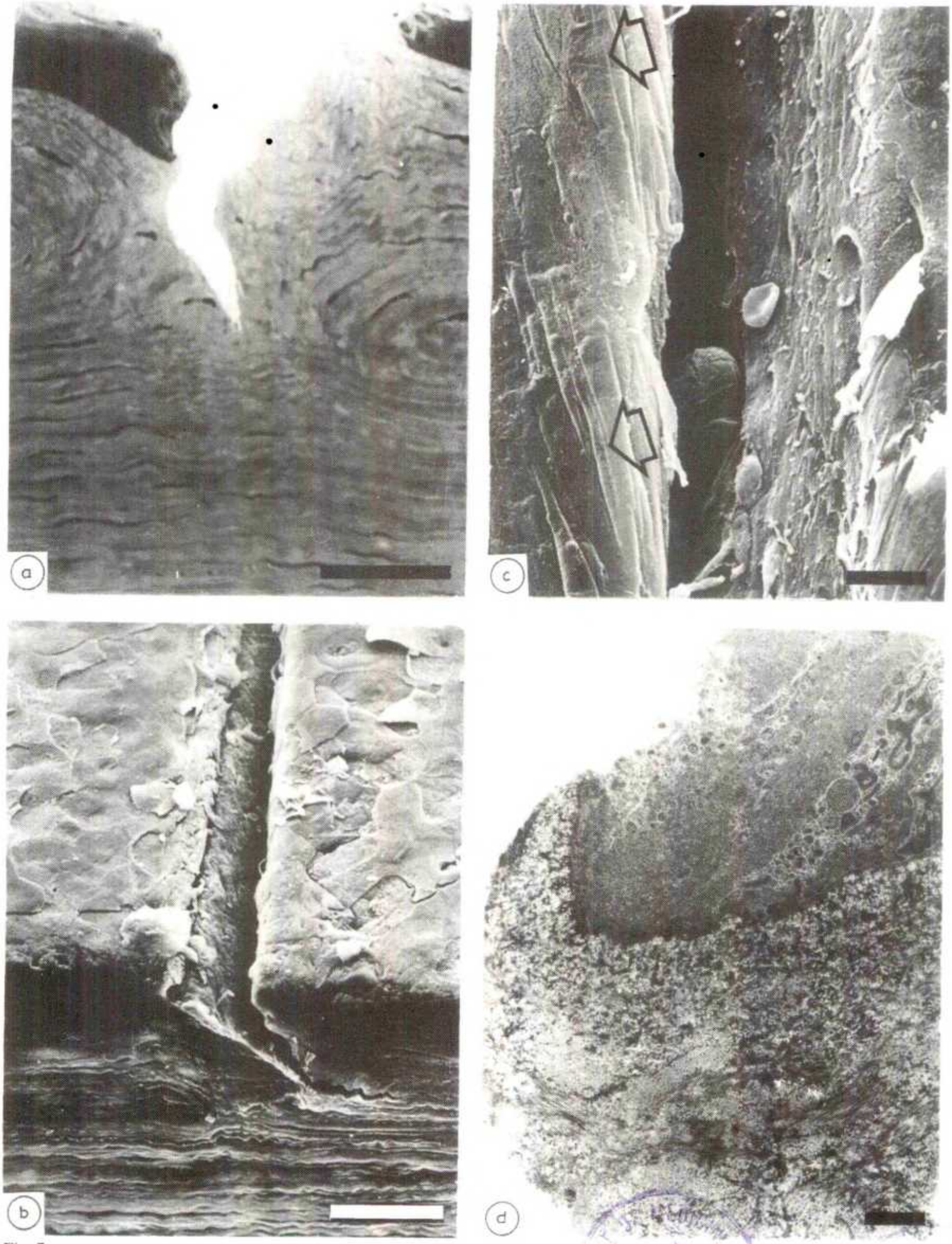

Fig. 7

difficult to assign such changes to those induced as a primary response to laser radiation and those that occurred as secondary tissue reactions or repair processes. One notable observation was that, wherever leucocytes had attached themselves to the walls of the troughs, the electron dense extralamellar component of the pseudomembrane was always absent.

All incised lamellae were swollen to between 2 and 2½ times that of normal lamellae. The degree of swelling was maximal immediately adjacent to the ablated edge and progressively decreased to become normal some 450–500 µm away from the wall of the incision. The individual collagen fibres in the cleaved portion of the lamellae increased in spatial separation to between 60 and 130 nm centre to centre as opposed to 45 to 60 nm in normal regions. In some lamellae the fibres at the ablated ends splayed or diverged, while in others there was a convergence or pinching together. These observations presumably give some indication of the states of tension that existed in any given lamella when it was cut, but in penetrating incisions the final picture may well have been modified by the two ablated ends moving against each other. The movement between the two portions of an individual lamella cleaved by ablation was frequently identified by the acute changes in orientation of collagen fibres in a specific stratum on either side of the incision.

Krypton fluoride laser irradiation (248 nm)
The first and most striking observation was that the line of ablation was no longer the confined rigidly linear plane seen at 193 nm but a meandering ragged edged gash. Secondly, the borders of the ablated zone were not sealed by pseudomembranes.

In TEM preparations the cleft within the zone of ablation was filled with a flocculent, relatively electron dense exudate containing fragments of collagen fibrils and isolated membrane profiles (Fig. 8b). The flocculent condensate was most compact within the central portion of the cleft, but then merged to give rise to a less compacted and less electron dense zone adjacent to each margin. In turn the pale zone was bordered externally by a morphologically distinctive dark band 2 µm to 3 µm in width, consisting of swollen and denatured collagen fibres (Fig. 8b). The width and the substructure of the band of denatured collagen was constant throughout the entire depth of all the ablations. On entering the distal aspect of the dark band normal collagen fibres doubled in diameter from about 30 nm to 60 nm, and at the same time an axial change in fibre direction occured (Fig. 8b). It was this band of swollen, denatured, disorientated, and splayed collagen fibres that gave such a ragged edged appearance. As with 193 nm irradiations, all incised lamellae were swollen immediately adjacent to the ablated edges, but at this wavelength other disturbances were also noted in a zone extending some 15 to 20 µm from the ablated edge. These ranged from areas of undulating or extremely disorientated collagen fibres, to isolated foci of swollen and electron dense elements like those in the dark band. Where keratocytes had been cleaved, the isolated remnants assumed an extreme electron density at the distal margin of the dark zone, and this was maintained up to 10 µm into unirradiated tissue. In such damaged cells no organelles could be determined within the denatured cytoplasm, and in many cases vacuolation occurred around the cell remnants and displaced the adjacent lamellae.

As in argon fluoride exposures, where incisions involved the limbal vessels, blood cells were seen throughout the ablated cleft.

Conventional incisions
Diamond. Stromal incisions executed with the diamond knife displayed minimal disturbance to adjacent tissues. Remote from the surface layers the line of any incision was difficult to detect, and in some cases was only disclosed by dislocations in the strata formation of lamellae. In virtually all incisions the cut edges were closely associated, with the exception of a few subepithelial lamellae. In such superficial clefts a

Fig. 8 *Transmission electron micrographs of the stromal aspects of incisions through rabbit corneas induced by* (a) *an argon fluoride excimer laser;* (b) *a krypton fluoride excimer laser;* (c) *a Micra diamond knife; and* (d) *a Sharpoint steel blade.* (a) *Shows two distant changes in relation to this incision, an extralamellar zone of high electron density or pseudomembrane (open arrows), and a somewhat larger but less electron dense intralamellar zone (closed arrows).* (b) *Shows more diffuse and extensive changes, with the cleft being full of flocculent deposits and bordered by the dark zone (arrowed) of swollen and disorientated collagen fibres.* (c) *The course of this incision (arrowed) is difficult to trace, as the edges of the wounds induced by diamond knife routinely closed.* (d) *Stromal incisions induced by steel blades always contained isolated fragments of collagen fibres (arrowed). The bar markers are 1 µm.*

Fig. 9 *Scanning electron micrographs of the endothelial cell surface of rabbit corneas in areas colinear with deep stromal incisions induced by* (a) *an argon fluoride and* (b, c, d) *a krypton fluoride excimer laser. In* (a) *the eye remained in situ for about 30 minutes after exposure, and pseudopodia are beginning to emerge from the endothelial cells whose borders are adjacent to the region of cell loss. A spectrum of change ranging from badly damaged cells* (b) (c) *to areas of cell loss* (d) *was a common observation with deep incisions at 248 nm. The bar markers are* (a) *25 µm,* (b) *250 µm,* (c) (d) *50 µm.*

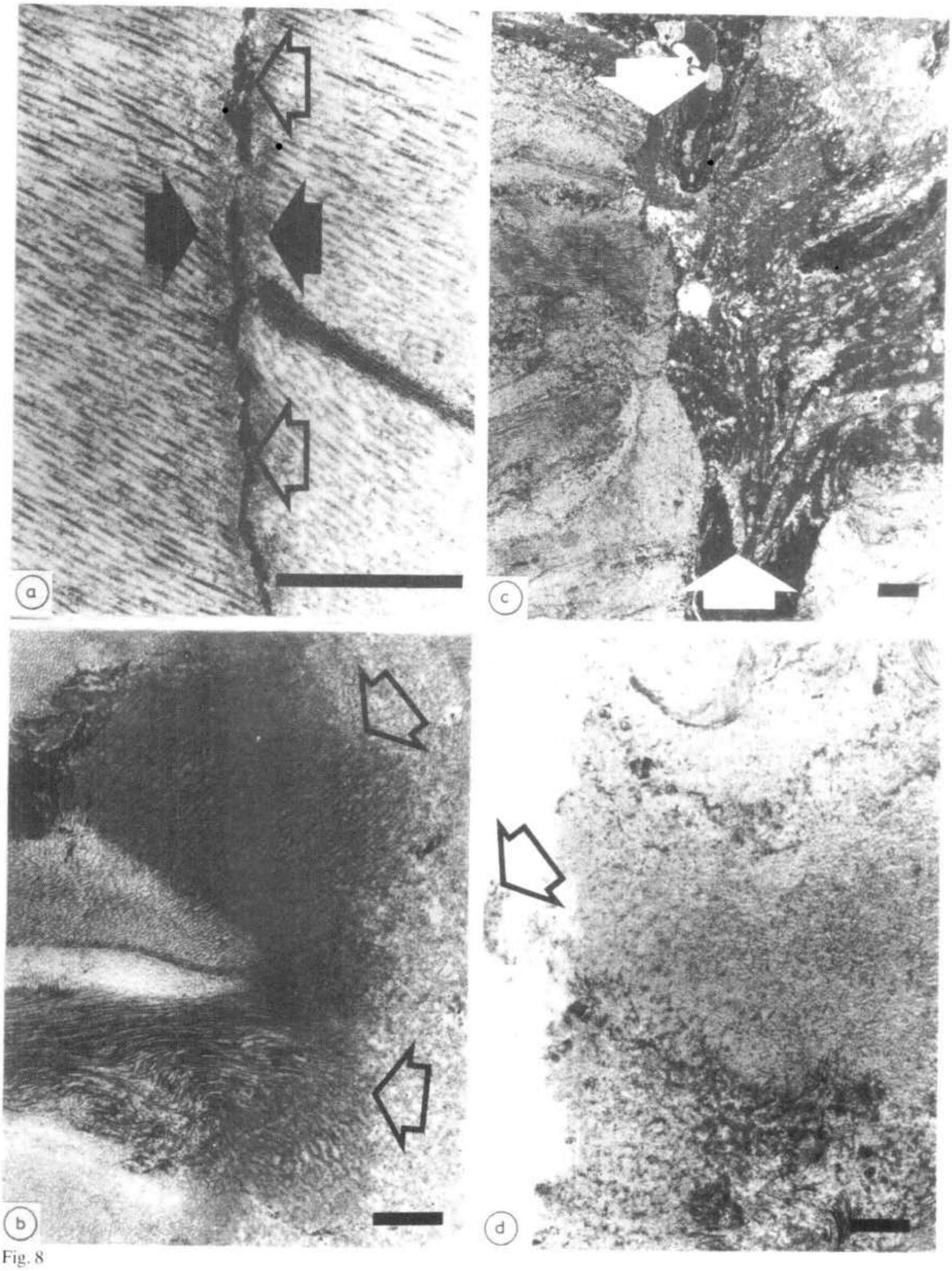

Fig. 8

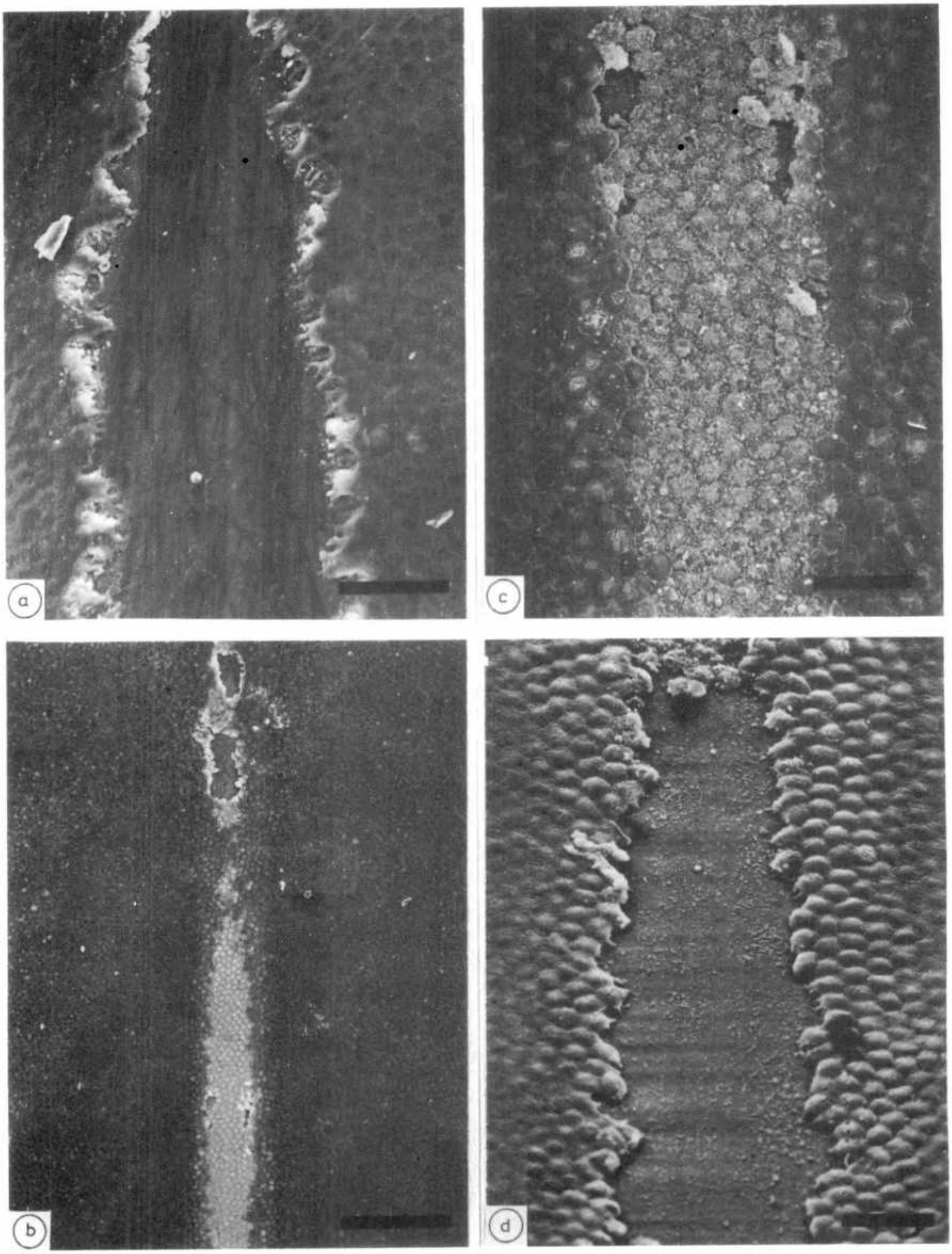

Fig. 9

similar electron opaque exudate to that seen in krypton fluoride ablations was apparent, but the substructure differed in that only a slight increase in electron density occured adjacent to the cleaved stromal edges (Fig. 8c).

No changes in diameter, staining properties, or orientation were determined in the collagen fibres of transected lamellae, although in some cases the fibres splayed slightly at the plane of incision.

Steel. The asymetric V-shaped grooves characteristic of incisions induced by steel blades, did not contain any electron opaque or flocculate material. In all such preparations the only content of the clefts was dislocated collagen fibres, either isolated or in bundles (Fig. 8d). On both edges of all steel blade incisions the cleaved lamellae were displaced towards the posterior surface of the cornea. Like incisions induced by the diamond knife, damage to the lamellae was not accompanied by gross changes in the staining properties or dimensions of the collagen fibres involved.

The vertex of clefts produced by steel blades were complex in that there was always evidence of blunt trauma or tissue displacement by splitting. This change in mechanism from cutting to compressional ripping was supported by the observation that steel blade incision ended in fissures extending along the strata between lamellae and at right angles to the axis of the cut.

DESCEMET'S MEMBRANE AND THE ENDOTHELIUM

None of the incisions produced with diamond or steel knives were sufficiently deep to damage either of these two layers. However, a surprising result was obtained in relation to non-penetrating ablations by both wavelengths of laser radiation. SEM preparations demonstrated endothelial cell loss along the line of some incisions even when Descemet's membrane had not been severed (Fig. 9). We had too few samples to determine the critical depths at which such loss or spalling of cells began to occur, but from our limited observations the floor of the trough had to be closer to Descemet's membrane than 40 μm at 193 nm and 60 μm at 248 nm.

Argon fluoride laser irradiation (193 nm)

In ablations closer to Descemet's membrane than 40 μm, typically Descement's was denuded of cells in linear swathes 5 to 12 (100–240 μm) cells across and whose long axis was coincident with that of the incision (Fig. 9a). The surface topography of endothelial cells bounding this area depended on the time that had expired between irradiation and fixation of the tissue. In those samples fixed within minutes of exposure the boundary cells had relatively sharp angular borders whose geometry seemed to mirror that of lost cells. If eyes were left in situ for longer than 30 minute after irradiation, this topography had changed such that the previously angular borders of the boundary cells had transformed into irregular, long, flat pseudopodia (Fig. 9a).

In sections, linear discontinuities were seen in Descemet's membrane both with and without penetrating damage to the overlying stroma, and in most cases it was relatively easy to discriminate between such radiation induced damage and perturbations due to preparative artefact. In penetrating incisions the ablated margins of Descemet's membrane were sharp and appeared little altered in terms of electron density, and coiled outwards towards the epithelial surface. In a few samples Descemet's membrane had broken as a result of inappropriate handling during processing. These artefacts were distinguished as the endothelial cells in such regions had fissures extending either around their hexagonal cell borders or straight across the cells cytoplasm.

Krypton fluoride laser irradiation 248 nm

Some endothelial cell lesions at this wavelength were similar to those described at 193 nm in terms of both morphology and dimensions. In addition some lesions were observed in which rectilinear areas of endothelial cell damage, rather than cell loss, were apparent (Fig. 9b, c). These lesions were of variable length, in excess of hundreds of μm, and maximally 5 to 8 cells in width. In SEM preparations affected cells appeared lighter than the normal surrounding endothelial population. On higher power observation damaged cells were flattened, had lost definition in relation to their cell borders, and had their surface membrane covered with spherical particles, presumably debris. In places individual cells or groups of cells were lost from the surface of Descemet's membrane within such lesions, and in these locations debris was present on the surface of the denuded membrane itself (Fig. 9d).

Discussion

This study is concerned with the acute effects induced in corneal tissues by incising them with a number of different agents.

We employed conventional incising devices in order to establish a data base using our tissue preparation procedures, against which to compare the unknown elements of damage induced by ultraviolet laser irradiation. In reality, although the scalpel has been a fundamental tool in surgery for many centuries, little is known about the physics of cutting tissues when considered at a molecular or atomic level. It is therefore difficult to relate the physical forces required to move the blade of a scalpel through biological tissues to the forces that are overcome in pushing disturbed molecules or molecular fragments apart. We do not know if there are preferred lines of cleavage at a cellular level within biological membranes or systems, nor do we know details of the chemical trauma that such molecular cleavage must induce. At a gross level our results confirm those of previous workers, that diamond knives appear to cut tissues[10-12] whereas steel blades seem to tear them via a shearing action.[13-15] This difference in mode of operation is related to a number of physical differences in the structure of the two blades. The edge of a diamond blade is formed from a crystaline matrix which is extremely hard, perfectly smooth, and impermeable. The angles of bevel on the blades vary according to preference, but the tips usually end in a slight radius and are maximally 0·1 μm in width. When new, diamond knives have cutting edges which display virtually no blemishes.[16] In contrast, steel blades are relatively soft and have a coarse textured surface that is comparatively porous. The cutting edge of steel blades is usually 1·5 μm in width, and even when freshly honed contains many blemishes and imperfections. While the greater tip width is important, surface imperfections on steel blades are the major contributors in increasing tissue resistance or drag factors encountered when making incisions with such devices. In turn, both the perturbations induced in the rate of motion of the blade by such resistance, and the relative movement of compressed tissue within the line of the incision and at right angles to it, cause problems in predetermining the depth of cut at any given point. We and others[11] have found that it is virtually impossible to incise tissue to a given depth, and therefore this must be a major deficiency in their employment in such procedures as radial keratotomy.[10 13-15]

On a cursory examination of the laser induced damage it is clear that a multifactorial induction process must be postulated, as no single damage mechanism could account for both the direct ablative effect in the incisions and the remote loss of endothelial cells beneath the troughs. Each of these two phenomena could result from a single but different damage mechanism, or each may be the product of the interaction of several such mechanisms.

Theoretically the following mechanisms may play a part in the ablation of tissue during the creation of incisions:

(1) Photoablation, or direct photon induced molecular decompensation.[6 7]

(2) Ultrafast thermal events, or photon-phonon interactions within the adsorption depth of the incident radiation.[5]

In contrast the loss of endothelial cells may be related to:

(1) Fluorescence and scattering from the absorbing volume of tissue, with the production of longer wavelength radiation that could be transmitted to, and absorbed by, deeper tissues.[17]

(2) Resonance induced in the posterior border of the cornea as a result of the pulse repetition frequency.

(3) Acoustic waves generated either by the explosive deposition of energy during ultrashort pulses or as a result of target recoil as tissue is lost from the irradiated surface.[18 19]

(4) Shock waves created by supersonic expansions, again related to energy deposition during ultrashort pulses.[20-22]

At a practical level it is extremely difficult to discriminate between the physical processes that may be involved in the ablation of tissue. Indeed so new is this technology in biological applications that we do not even possess accurate information on the transmission characteristics of far ultraviolet radiation—data which are essential for detailed biophysical analysis of mechanisms. So far published data on transmission and absorption coefficients for ocular media in the ultraviolet have been obtained by means of suitably filtered emission from mercury xenon sources. As a result no useful data exist for wavelengths shorter than 250 nm.[23 24] These studies did generate some useful general findings in that the high optical density of 4, between 200 and 295 nm, can be explained only by assuming a significant role in absorbing this radiation by proteins and collagen; for example, peptide bonds present in the cornea will absorb at 190 nm. This is in direct contrast to absorption of infrared radiation, where water is the principal absorber.[25] The high absorption, or short penetration depth, of ultraviolet radiation means that transmission figures cannot be determined for the intact cornea—that is, insufficient radiation passes through it to be measured.

Several workers have recently made measurements using frozen sections of corneal tissue, and two sets of data are currently being discussed. Puliofito (personal communication) estimates that the attenuation length in the cornea is about 1 μm at 193 nm and 3 to 5 μm at 248 nm. In contrast, Hillenkamp (personal communication) claims measured figures of 3·5 μm at 193 nm and 33 μm at 248 nm respectively.

Observations on the stroma in the present study could give rise to some unfortunate misconceptions, as for example, the lateral spread of tissue damage associated with the ablation process is 300 nm at 193 nm; and 2 to 3 μm, the dimension of the dark band, at 248 nm. If such dimensions were assumed to be related to the penetration depth of laterally scattered photons, they would seem to offer circumstantial evidence in support of Puliofito's claims. However, such an assumption would be incorrect, as these damage zones do not correspond to the total photon absorption depth but that fraction of the depth at which the fluence is sufficient to cause significant damage. In a recent quantitative study looking at the photochemistry of bond cleavage in both polymethylmethacrylate (PMMA) and collagen induced by irradiation at both 193 and 248 nm, the most conclusive evidence for an underlying mechanism of photoablation has been provided, and the figures of Hillenkamp best fit the experimental data.[26] In these experiments Srinivasan and his coworkers measured the depth of tissue etched per pulse as a function of the fluence generated by each pulse, and at the same time they chemically analysed the molecular moities generated by the ablation process. Their findings were highly significant and will be fundamental to future work in this field. In summary they have discovered the following:

(1) The etch depth per pulse was 10 times greater at 248 nm than at 193 nm, which approximately matches the inverse ratio of the absorptivities at the two wavelengths (Hillenkamp's data). This accuracy of dose versus tissue loss or cutting depth has recently been exploited in a series of experiments to test the viability of 193 nm irradiation in radial keratotomy in human cadaver eyes.[27]

(2) The mass of material ablated per joule of energy absorbed within the ablated volume was similar at both wavelengths.

(3) When the etch depth per pulse was plotted as a function of the fluence of pulses, a similar shaped curve was obtained for each wavelength, and each curve could be subdivided into three regions. In the first part of the slope of the sigmoid curve the fluence is low, and effectively below true ablation, threshold fluence. The second part of the curve rises rapidly and accounts for efficient ablation being a region where 20 to 90% of the incident photons are absorbed within the ablated volume. Finally, a flattening tail suggests a loss of potency of ablation due to the occurrence of secondary photolytic processes. All of our irradiations were carried out in the true ablation region.

(4) The chemical products of photomolecular decompensation of PMMA are the same at both wavelengths, carbon dioxide and methylmethacrylate (MMA),[28] but the proportions generated are quite different.[26] At 193 nm 18% of the ablated polymer is broken up into MMA or oligomers of low molecular weight. In contrast, at 248 nm less than 1% appears as MMA, and the predominant products are a mixture of high molecular weight oligomers. Similar results were obtained with collagen, with fragments of smaller molecular weight being produced by irradiation at the shorter wavelength. This finding is the key to the difference in edge quality seen in cuts throughout the present study.

(5) Debris expelled by irradiations at 193 nm was in the form of fluffy, cotton-like material, which was in contrast to the fused coalesced masses seen at 248 nm. These findings are confirmed in our study and imply that lower temperatures prevail at the shorter wavelength.

We would support the hypothesis of Srinivasan and his colleagues that excimer lasers induce their beam tissue interactions by photomolecular decompensation. In their thesis it is suggested that the ablation process requires a balance between the photon energy which determines the quantum yield for bond break, and the excess energy of the photon over the bond energy which is then available to expel the products at supersonic velocity. An ultrafast thermal process does not fit the observed kinetics and could not account for the different molecular proportions in the debris generated by the two wavelengths.

The process of photomolecular decompensation may have profound implications with respect to cutting biological tissues, as it seems to cleave organic bonds in a novel fashion. Both the mechanical transients associated with conventional cutting devices like diamond and steel, and thermal disturbances generated by laser photocoagulators, rupture bonds in the electronic ground state and therefore generate large zones of damage by secondary translocation of energy degrading processes. In contrast photoablation involves the electronically excited state of the bonds undergoing cleavage and is highly localised. The 'unzipped' molecules in the pseudomembranes of cells cleaved by irradiation at 193 nm may result in a sufficiently undisturbed interface on their distal aspect so that the cell remnant can, and clearly does, survive for some time after trauma (Fig. 4a).[29] This obviously does not happen with diamond or steel incisions, where cleaved cells die immediately, either through loss of their contents expelled through the cut surface or as a result of osmotic problems. Given the importance of chemogradients in inflammatory and healing responses, the focal nature of the ablation process may well result in an increased latency at the beginning of wound healing, both by virtue of the small volume of tissue damaged and the creation of an artificial barrier to diffusion of chemical markers. The pseudomembranes may also present short term physical barriers that limit the access of macrophages.

Having suggested that 193 nm is the wavelength of choice for further investigation of the surgical role of excimer lasers, and having excepted that tissue ablation occurs by a photochemical process, we believe it may be helpful to comment briefly on the safety considerations of such irradiations. At 193 nm the cornea is virtually opaque and therefore there is no risk to deeper structures. This does not hold for the longer wavelength excimer lasers, because between 308 nm (xenon chloride) and 350 nm (xenon fluoride) the cornea transmits significant amounts of the incident radiation.[30] The xenon chloride excimer laser could be called a 'cataract machine' because at 308 nm the threshold for lens damage is only about 1 J/cm². In the phakic eye only a trace amount of such radiation would reach the retina, but in an aphakic eye this figure rises to 50%, and it should be remembered 308 nm is near the peak of the action spectrum for solar UV induced carcinogenesis of the skin. The mutagenic effects of ultraviolet radiation have received much attention, and at present the most harmful wavelengths are considered to be those around the peak absorption of DNA, about 280 nm.[30] It is also interesting to note in this context that the minimum irradiance thresholds for photokeratitis are between 3 and 4 mJ/cm² and occur at 270 nm.[30]

In the present study doses of some hundreds of mJ/cm² were used but at a wavelength which the best evidence suggests is outside the mutagenic zone, and whose absorption depth limits penetration almost to the zone of ablation. Obviously we will be examining this question in more detail in the future, but currently we do not envisage major problems with mutagenesis.

The loss or spalling of endothelial cells beneath the line of irradiation is clearly a matter of concern in relation to potential surgical applications, and further experiments are under way at a variety of energy fluences to determine the critical ablation depth and dose configuration at which this complication arises (Fig. 9). Our current observations based on the geometry and dimensions of the area of cell loss suggest that these cells are compromised by mechanical (shock or acoustic) waves dissipating their energy at an interface of mismatch of acoustic impedance.[31,32] This concept is supported by our observations that endothelial cell damage is greater at 248 nm and occurs at this wavelength when erosion depths are farther from Descemet's membrane than when troughs are created by 193 nm radiation. This finding is significant because at the longer wavelength more tissue is eroded per pulse and the resultant mechanical waves are larger.[26] We do not consider the fluorescence induced by absorption of ultraviolet radiation within the ablation zone to have a significant role in endothelial cell loss.

In conclusion we feel that excimer laser radiation at 193 nm may have a future in microsurgery of the eye. It seems to ablate tissue by a novel photochemical process whose parameters can be controlled to incise tissue to precise depths with submicron accuracy. It now awaits further study to determine if any problems exist in relation to wound healing or mutagenesis.

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Use of penetrating keratoplasty in acute bacterial keratitis

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SUMMARY Twenty-three patients with bacterial keratitis had penetrating keratoplasties performed for deep indolent ulceration or descemetoceles, during the acute period. The period in hospital (17·6 days) was significantly lower than for a control group (35·4 days) who were treated medically and had subsequent grafts. The number of grafts remaining clear was similar, 70% and 72% respectively. Eleven patients (48%) of those who had an acute graft achieved corrected visual acuities of 6/12 or better. No cases of reinfection occurred and no eyes were lost.

With improved microsurgical techniques and instrumentation the success rate of corneal grafting has improved considerably. Despite this most surgeons are hesitant to operate on inflamed or infected eyes because of the danger of complications, including infection of the donor disc. However, on occasions an acute graft is vital to save the eyeball. Into this category fall corneal lacerations with loss of corneal tissue and ruptured descemetoceles unresponsive to medical therapy. Although not performed under ideal conditions we have found the outcome of these acute grafts to be satisfactory in many cases.

The medical treatment of indolent corneal ulcers and descemetoceles can be prolonged, requiring long periods of hospitalisation. The favourable outcome of corneal grafts in other acute conditions suggested that this could be a reasonable method of treatment for indolent ulcers and descemetoceles, especially if these disorders were central and likely to heal as heavily vascularised scars obscuring the visual axis, thus requiring a corneal graft at a later date.

Patients and methods

The management of patients admitted to this hospital with corneal ulceration follows a standard regimen.[1] Corneal scrapings are taken for Gram stain and culture. Initial broad spectrum antimicrobial therapy is instituted and modified later according to the laboratory findings. If corneal thinning occurs, a topical anticollagenase (acetyl cysteine 10%) is prescribed. Perforation is treated by fitting a soft bandage contact lens or by application of tissue adhesive. Failure to seal the defect is an indication for surgical intervention.

Patients with peripheral ulceration or descemetoceles, or those in whom the central ulceration was shallow and responded rapidly to medication, were treated as above. When descemetoceles or deep corneal ulcers were present centrally, the patients were offered a corneal graft as a primary procedure provided the following criteria were met. The lesion should be both small enough to be totally excisable, leaving a healthy rim of cornea, and be unresponsive, or slowly responsive, to therapy. All these lesions were such that, if treated medically, they were likely to heal leaving central corneal scars requiring corneal grafts at a later date. Twenty-five patients (17 men and eight women) received acute grafts, performed by the author, during the period August 1981 to April 1984. All had proved or presumed bacterial keratitis and 15 had descementoceles, three of which had perforated and not responded to medical therapy. The remaining 10 patients had central indolent corneal ulcers. Two patients from the descemetocele group failed to attend follow-up and were excluded from the study. A further group of 18 patients fulfilled the criteria for admission into the study but did not receive a graft initially. Either the patient refused operation or donor material was not available. This group (11 men and seven women) later received a graft and were used as a control group for our series.

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All corneal grafts were performed by a similar technique. Donor material was obtained from whole eyes preserved in a moist chamber at 4°C or from corneoscleral discs preserved in McCarey-Kaufman culture medium.[2] Donor corneal discs were cut 0·4 mm larger than the recipient bed, and secured with a continuous 10/0 nylon suture with a buried knot. No tissue matching was undertaken. Topical antibiotic therapy was continued and topical corticosteroids initiated postoperatively.

Results

Twenty-three patients received acute corneal grafts in this study; a further 18 patients with similar corneal disease, who had secondary grafts, are included as controls. The ages of the two groups were almost identical (Table 1) but there were relatively more females in the control group.

In the acute group 10 patients had indolent ulcers and 13 descemetoceles, two of which had perforated. Thirteen patients in the control group had indolent ulcers and five had descemetoceles.

The average period in hospital for the acute graft group was 17·6 days compared with 24·7 days for the control group, whose disease was treated medically. The subsequent admission for an average of 10·7 days for a secondary graft gave a total mean period in hospital of 35·4 days for the control group.

Twelve grafts in the acute group developed rejection episodes; these were reversed in six patients. From the control group eight patients had rejection episodes, but only three were reversible. Therefore 26% of the study group and 28% of the control group grafts were lost from rejection. Only one case of primary graft failure occurred, and this was in the study group. Considering all causes of graft failure, 70% of the acute grafts remained clear compared with 72% of the secondary control grafts. A number of patients in each group had a subsequent graft that was successful. These results are not included in this paper. The mean follow-up time was 20 and 23 months for the acute and control groups respectively.

A number of complications arose in the acute graft group (Table 2). Many of these problems were present at the time of operation and were related to the disease rather than the surgery. Apart from the six grafts that became opaque from irreversible rejection, a further graft developed marked stromal haze in the early postoperative period, attributed to primary graft failure. Two other grafts developed mild stromal haze following reversible rejection episodes.

Table 1 *Clinical details and results of grafting*

	Acute graft group (n=23)	*Secondary graft group (n=18)*
Sex M:F	15:8	11:7
Age		
Average	44	48
Range	18–64	19–71
Indolent ulcer	10	13
Descemetocele		
Intact	11	5
Perforated	2	—
Hospital admission (days)		
Initial (range)	17·6 (12–19)	24·7 (11–35)
Secondary	0	10·7 (9–13)
Total	17·6 (12–19)	35·4 (22–46)
Rejection		
Reversible	6	3
Irreversible	6 (26%)	5 (28%)
Total	12 (52%)	8 (44%)
Clear grafts	16 (70%)	13 (72%)
Follow-up (months)		
Mean (range)	20 (8–34)	23 (12–40)

Table 2 *Complications*

Stromal haze	3
Cataract	5
Pupillary membrane	3
Posterior synechiae	7
Anterior synechiae	6
Glaucoma	4
Stepping	2
Resuture	1
Astigmatism >4·5 D	6
Graft infection	0

Significant lens opacities developed in five eyes; in three these were present at operation and were associated with posterior synechiae and pupillary membranes. One patient (Fig. 1) had a lens abscess and an extracapsular extraction was performed at the time of grafting. A further patient developed a cataract (Fig. 2) six months later, and an extracapsular extraction was then performed.

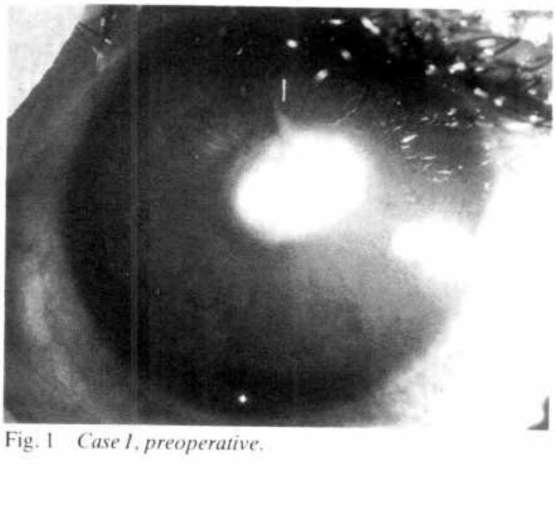

Fig. 1 *Case 1, preoperative.*

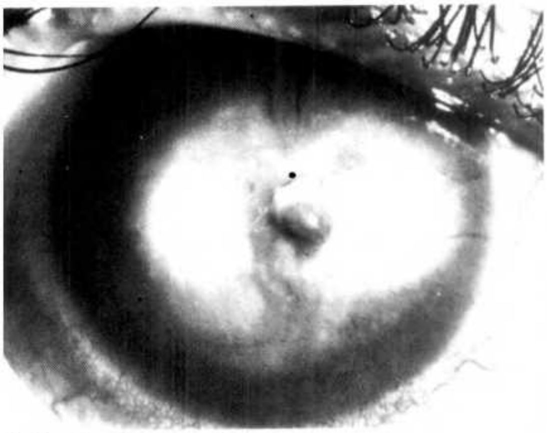

Fig. 2 *Case 2, preoperative.*

Inflammatory pupillary membranes were found in three patients. The membrane was left intact in one patient, but further synechiae developed causing pupil block glaucoma and iris bombé. A broad iridectomy with lens extraction was performed four weeks post graft. The other two pupillary membranes were removed at the time of grafting together with extracapsular lens extraction, because of anterior lens opacities. In addition to these three cases a further four patients developed posterior synechiae without sequelae.

Anterior synechiae developed in six patients. In two of them sodium hyaluronate was used to divide the synechiae in the early postoperative period. Three of these eyes developed glaucoma, and all were controlled with medical therapy. Glaucoma also occurred in the patient mentioned above with posterior synechiae and pupillary membrane.

In two patients stepping of the graft occurred owing to sutures 'cheese wiring.' In one resuturing was necessary. Both cases developed unacceptably high degrees of astigmatism, defined as a refractive astigmatism of greater than 4·5 dioptres. A further four patients developed excessive astigmatism; in two surgery had been performed on soft eyeballs with perforated descemetoceles. No cases of graft infection or endophthalmitis occurred.

In the 16 eyes that maintained clear grafts the final visual outcome varied (Fig. 3), because of complications such as minor lens opacities, stromal haze, or retinal problems. However, 11 (48%) patients achieved corrected visual acuities of 6/12 or better.

CASE HISTORIES

Case 1. A 36-year-old male injured his right eye with a piece of wood, sustaining a penetrating corneal wound. Two days later he had a central corneal abscess and a swollen infected lens (Fig. 1). Gram stain revealed scanty Gram-positive cocci but no growth was obtained. Topical and subconjunctival gentamicin and cephamandole were given, but the abscess slowly progressed. These two agents were then given systemically, whereupon the disease remained stationary. Sixteen days after admission a 7·5 mm graft was performed, a small hypopyon washed out, and an extracapsular lens extraction performed.

There were no postoperative complications and he left hospital nine days later. His graft has remained clear (Fig. 4) achieving a visual acuity of 6/7·5 (+13·75/+2·25×125°), follow up 17 months.

Case 2. A 41-year-old woman gave a three-month history of a sore right eye that had been treated by her general practitioner. The cornea had a central abscess and descemetocele (Fig. 2). An 8·5 mm corneal graft was performed after two days of

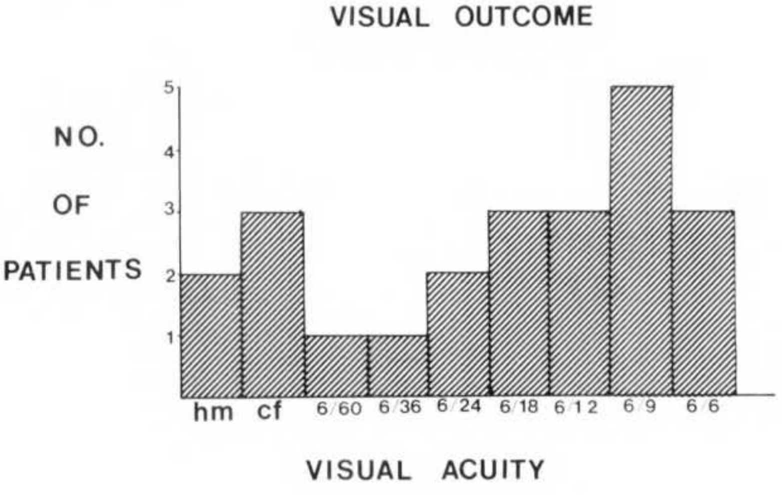

Fig. 3 *Visual outcome of patients receiving acute full-thickness grafts.* hm=*Hand movements.* cf=*Counting fingers.*

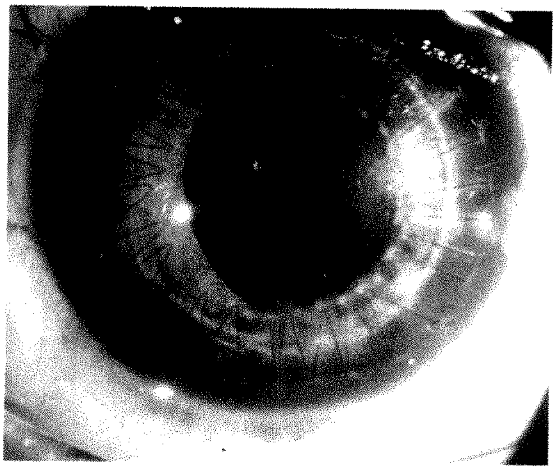

Fig. 4 *Case 1, postoperative.*

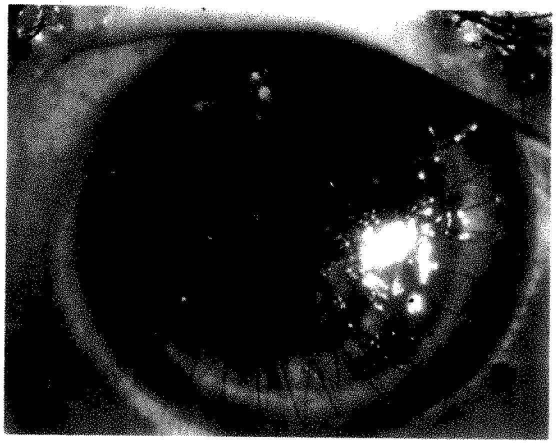

Fig. 5 *Case 2, postoperative. Posterior synechiae and early anterior lens opacities are visible.*

intensive topical gentamicin and cephamandole; no organisms were seen on Gram stain and there was no growth on culture. Recovery was uneventful, and she left the hospital nine days after admission. A small area of posterior synechiae formed, and she developed lens opacities (Fig. 5). An extracapsular lens extraction was performed six months post grafting. One month after lens extraction she developed a rejection response that was reversed, and her visual acuity remained at 6/12 (+10·50/−3·00× 180°) after a follow-up period of 21 months.

Discussion

Corneal ulcers can take a considerable time to heal despite being amenable to many forms of treatment that should ensure high tissue concentrations of therapeutic agents. Similarly patients with descemetoceles may need prolonged periods in hospital before the defect heals. In our control group, treated medically, an average of 24·7 days in hospital was required. After healing, a vascularised cornea often remains, which will increase the likelihood of rejection of a subsequent graft.

The surgical maxim recommending removal of dead or severely damaged tissue—for example, incising and draining an abscess—is as relevant to the cornea as elsewhere in the body. Even if the offending organism has been eradicated, various toxins and enzymes remain, resulting in further damage and the prevention of healing. Excision can be effected by keratoplasty. If the patient is likely to need a graft at some stage to restore vision, it is a reasonable proposition to perform this as soon as possible to allow early rehabilitation. Initially the diseased cornea is not vascularised. Therefore grafting at this stage may not be associated with a high incidence of rejection. Although the eyes are inflamed, we have found the inflammation quickly subsides once the diseased cornea is excised.

Although keratoplasty has been used in fungal keratitis by a number of authors,[5-6] this mode of treatment has not been widely reported in bacterial keratitis. Sporadic use of lamellar keratoplasty has been reported.[7-11] Penetrating grafts have not been widely used in the past.[10 12]

Two more recent, larger series[13 14] have used both lamellar and penetrating keratoplasties in bacterial keratitis. We have been unhappy with the use of lamellar grafts in this condition because of the danger of reinfection. Malik and Singh[13] reported recurrence of infection in all eight of their lamellar grafts, and one eye was lost. Du *et al.*[14] used lamellar grafts if the infection was superficial. In our study lamellar grafts were not used; all corneas had deep stromal involvement. Patients with superficial disease were not offered surgery. We have found these infections to be less virulent and more responsive to medical therapy.

The average period in hospital for the acute graft group (17·6 days) was over a week less than for the control group (24·7 days). If we consider the subsequent admission for a secondary graft, the total mean period (35·4 days) becomes almost twice that for the acute graft group. Therefore early grafting decreases hospitalisation significantly and allows for early rehabilitation. 70% of the acute grafts remained clear compared with 72% for the control group and 67% in the penetrating keratoplasty group of Du *et al.*[14] (n=38). It would appear that early surgery does not jeopardise the final outcome of the graft. The incidence of rejection was higher in the acute group (52%) compared with the control group (44%), though the failure rate from rejection is similar in the two groups, 26% and 28% respectively.

Rejection was more difficult to reverse in the control group, and this may be related to the increased corneal vascularisation.

The number of complications is quite large, as would be expected in surgery of this type. However, as mentioned earlier, many of the complications are related and occurred in the same eye. The pupillary membranes were all associated with posterior synechiae, and all cases of glaucoma had anterior synechiae. One case of stepping required resuture and both developed excessive astigmatism. In this regard better results could have been obtained by operating before the descemetocele perforated. Unfortunately some patients present with leaking corneas and flat anterior chambers, and these require urgent surgery if they are unresponsive to medical therapy. There were two such cases in this series: both developed complications of anterior synechiae —glaucoma, unacceptable astigmatism, and in one a pupillary membrane with cataract. These patients, who required urgent surgery to salvage the eyeball, were operated upon for different criteria than the other patients. The equivalent in the control group does not of course exist, so their inclusion introduces a bias that makes comparison of complications inappropriate. If these two patients were excluded, the overall complication rate for the acute graft group drops considerably.

This study indicates that early grafting offers the advantage of shorter periods of hospitalisation and early rehabilitation. There may be an advantage in operating before vascularisation becomes established, but overall the final graft outcome does not differ significantly from that in a similar group of patients who were treated medically and had subsequent grafts to restore visual acuity.

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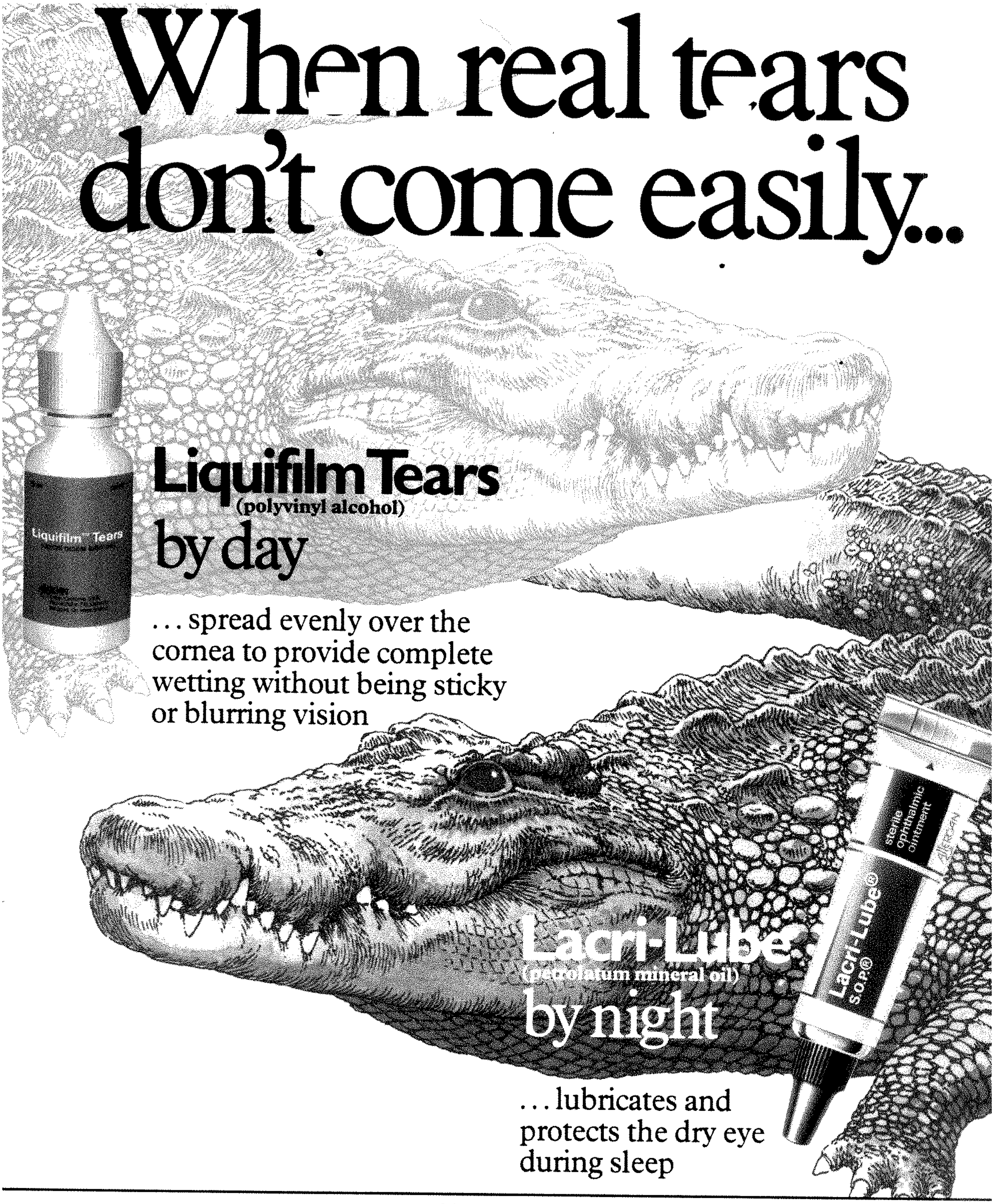

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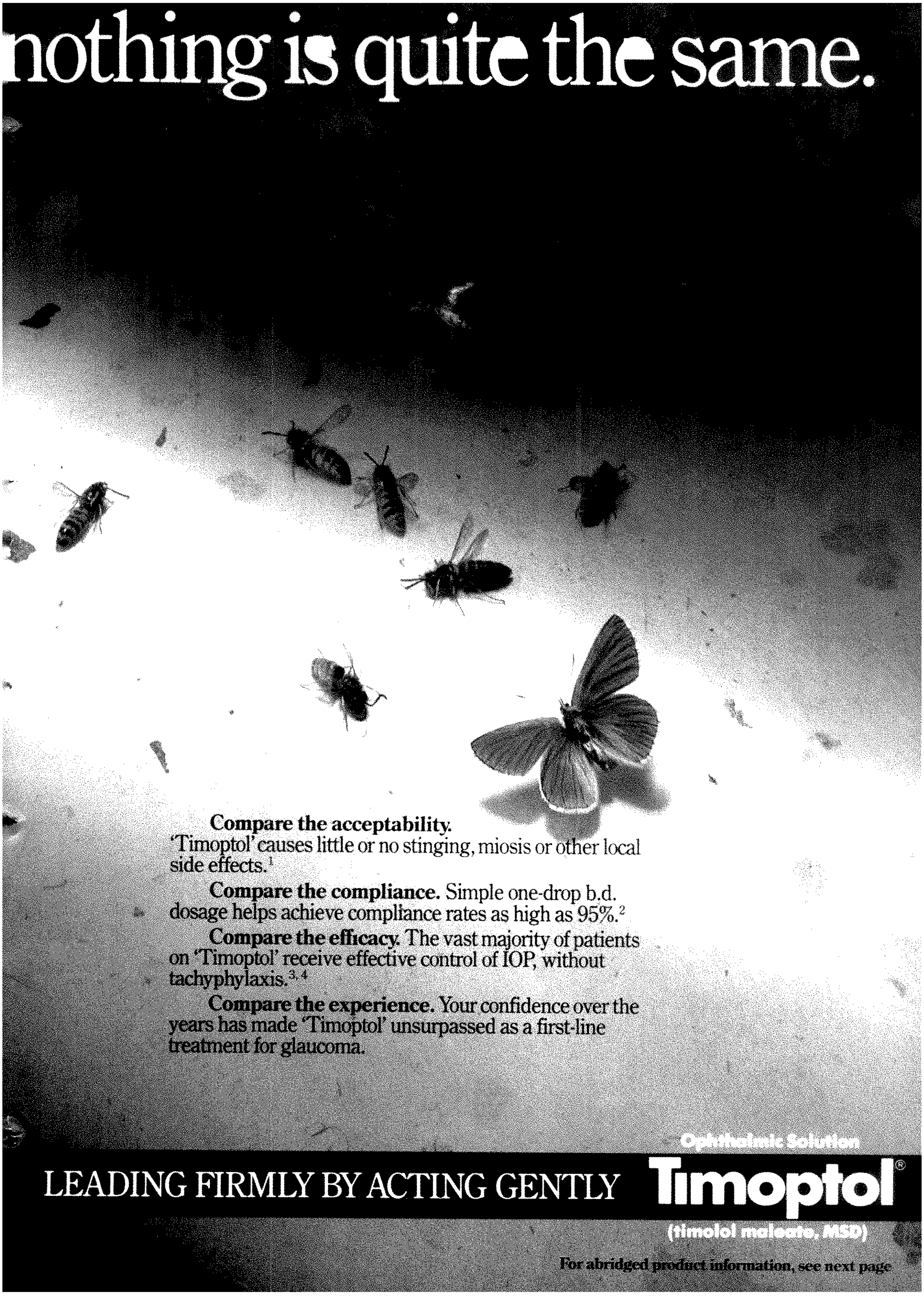

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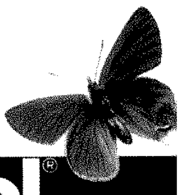

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British Journal of Ophthalmology, 1986, **70**, 507–509

Experimental contamination of Minims of fluorescein by Pseudomonas aeruginosa

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SUMMARY Contamination of fluorescein solutions by *Pseudomonas aeruginosa* has been a concern of ophthalmologists for many years because of the severity of pseudomonas keratitis. Attempts to prevent contamination have been directed at stringent sterility control during manufacture and the introduction of single-dose disposable containers such as Minims. Deliberate contamination of Minims fluorescein with *Pseudomonas aeruginosa* was attempted. Under conditions likely to be met with in clinical practice the contents remained sterile. However, under extreme conditions of immersion in pure broth culture of *Pseudomonas aeruginosa* contamination could be achieved. The relevance of these results to clinical practice is discussed.

Contamination of fluorescein solutions by *Pseudomonas aeruginosa* has long caused concern[1,2] because of the severity of pseudomonas keratitis.[3] Fluorescein solution is widely used to delineate corneal epithelial deficits,[4] particularly in casualty departments, where superficial anterior segment trauma is commonly seen.[5,6] The corneal epithelium is a natural anatomical barrier to infection, and defects whether due to trauma (abrasions), virus infection (dendritic ulcers), or degeneration (ruptured bullae) are portals to the stroma for bacterial pathogens.

Although the commonest cause of a central corneal ulcer is herpes simplex,[7] bacterial corneal ulcers still occur frequently, and, of these, *Pseudomonas aeruginosa* keratitis is the most common.[3] Since fluorescein solutions are known to be capable of contamination with *Ps. aeruginosa*,[1,2] considerable effort has been spent on minimising the risk of an already compromised cornea receiving an inoculum of pseudomonas when fluorescein is applied. One result has been the introduction of single-dose disposable containers of fluorescein such as Minims and others. While reputable and conscientious pharmaceutical companies will ensure that the fluorescein is sterile when dispatched from the point of manufacture, the risk of accidental contamination at the point of use does not appear to have been previously assessed.

Materials and methods

Fluorescein Minims consist of 1 or 2% preservative-free fluorescein in a polypropylene Minims bottle which tapers to a neck. The neck and exit pore are covered by a polypropylene cap. A paper and polypropylene overwrap enclose the bottle and cap.

Experiment 1. One hundred Minims of 2% fluorescein were removed from their overwraps and immersed in a broth culture of $5{\cdot}5 \times 10^8$ colony forming units (cfu) per ml of a recently isolated strain of *Pseudomonas aeruginosa.* After 5 minutes the bottles were removed, shaken dry, the caps carefully removed, and a single drop of the fluorescein plated on to nutrient agar. Great care was taken to ensure that no drop of broth on the bottle was allowed to run up the neck after this had been exposed. The agar plates were cultured at 37°C for 24 hours, at which time any growth of pseudomonas was considered to represent contamination of the fluorescein. As with subsequent experiments, appropriate control plates were used to check for aerosol contamination of culture plates.

Experiment 2. One hundred Minims of 2% fluorescein in overwraps were immersed in a broth culture of $9{\cdot}5 \times 10^6$ cfu per ml of a recently isolated strain of *Ps. aeruginosa*. After 5 minutes they were removed and shaken dry. Each overwrap was opened, the Minims

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bottle removed, and a single drop of the fluorescein plated on to nutrient agar, which was incubated as in experiment 1.

Experiment 3. One hundred Minims of 2% fluorescein were subdivided into two equal groups, one of which had the overwraps removed. With surgical gloves worn the hands were contaminated by immersion in a broth culture of $8\cdot5 \times 10^5$ cfu per ml of a recently isolated strain of *Ps. aeruginosa* and then lightly dried. A single drop of fluorescein was then plated on to nutrient agar from each Minims bottle, the overwraps being removed where necessary. After every 10 operations the gloves were discarded, cultured, and a new pair contaminated in an identical fashion before proceeding. Incubations were as in experiment 1.

Results

The results are presented in Table 1. It can be seen that direct immersion of Minims bottles (experiment 1) in broth culture of *Pseudomonas aeruginosa* resulted in contamination of the vast majority, but that the presence of the paper and polypropylene overwrap in experiment 2 reduced this to only a few contaminated. When the bottles were manipulated with gloves contaminated with *Ps aeruginosa* (all of which were culture proved) the rate of contamination was reduced yet further irrespective of whether the overwrap had been previously removed.

Discussion

When Minims bottles of fluorescein are removed from their overwraps and immersed in high titre broth cultures of *Pseudomonas aeruginosa,* the first drop of fluorescein used is contaminated in the overwhelming majority of cases. It seems unlikely that the organism would be able to penetrate the relatively thick polypropylene walls of the Minims bottle. Since care was taken to ensure that drops of broth did not run down the side of the bottle and along the neck, this can also be discounted as the cause of the contamination. It is more probable that a meniscus of pseudomonas-contaminated broth was formed at the base of the neck adjacent to the opening of the cap. When the cap was removed, the meniscus would be smeared along the neck to the exit pore. This mechanism for contamination of eye drops has previously been described.[8,9] Preliminary experiments (data not shown) suggest that, if the broth is painted on with a bacteriological loop rather than immersion of the bottle, then the contamination rate is reduced to the very low levels seen in experiment 3. This provides further support for the suggested mechanism of contamination.

Table 1 *Number of plates of nutrient agar which grew* Pseudomonas aeruginosa *after 24 hours' incubation at 37°C. In experiment 3a the overwraps were removed prior to manipulation by contaminated gloves, whereas in experiment 3b they were removed by the infected gloves*

Experiment	*Number of plates which grew* Pseudomonas aeruginosa
1	99
2	3
3a	0
3b	0

The presence of an intact overwrap significantly reduces the incidence of contamination after immersion in broth culture. Contamination probably occurs when the pseudomonas broth leaks through the paper section of the overwrap, producing a situation identical to that found in experiment 1. When contamination was attempted by using infected hands (gloves) to manipulate the Minims bottles, the level of contamination of the fluorescein was reduced to a very low level irrespective of whether the overwrap was previously removed or not.

Whereas contamination of the fluorescein could regularly be obtained by immersing Minims bottles in a high titre broth of pseudomonas, it seems inconceivable that such a situation would arise in clinical practice. Furthermore, the inoculum required to produce disease in the human eye, and the size and frequency of such inocula are unknown. A recent study in hospital staff has shown that *Ps. aeruginosa* is capable of colonising the skin under wedding rings,[10] thus creating a situation analogous to experiment 3. Since no contamination of fluorescein was produced by manipulation with experimentally contaminated gloves, it may be concluded that this potential reservoir of infection is not a significant risk to patients.

This study was funded in part by the Wellcome Trust. I should like to thank Dr Graham Hopkins of Smith and Nephew Pharmaceuticals Ltd for helpful discussions and supplies of Minims. The technical assistance of the following has been invaluable: Mrs Christine Harber, Mr Tim Hodges, and Mr Paul Strickland. Mr Andrew Elkington, FRCS, and Miss Katherine Stevenson, FRCS, contributed helpful discussions, and I should like to thank Dr Bill Blyth and Professor David Easty, FRCS, for reading the manuscript.

Minims is a trade mark of Smith and Nephew Pharmaceuticals Ltd.

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Clinical assessment of corneal endothelial cell density: an original system of grading using a slit-lamp biomicroscope

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SUMMARY An original system of grading of the corneal endothelial specular reflection, as assessed with a Haag-Streit 900 slit-lamp biomicroscope, has been shown to have a very highly significant relation to the endothelial cell density measured by contact specular photomicroscopy. The grading, though subjective and therefore not a substitute for the detailed record of photomicroscopy, is readily applicable to clinical practice and is a useful method of comparing and recording endothelial cell densities when assessed by the same observer. The intraobserver, but not the interobserver, variability has been examined, and the theoretical aspects of the grading system and a clinically applicable interpretation of the grading are presented.

With the introduction of specular microscopy of the corneal endothelium into clinical practice,[1] there came a widespread recognition of the loss of endothelial cells that could occur with anterior segment surgery,[2-4] and of the development of corneal oedema and bullous keratopathy as a consequence of lower endothelial cell densities (ECDs). The ECD below which corneal decompensation becomes probable is poorly documented but is thought to be approximately 500 cells/mm^2.[5-8]

There still remains a need to assess the ECD of an eye prior to surgery despite markedly improved techniques of microsurgery and surgical instrumentation over the last decade. This need is not only to detect those eyes at risk of postoperative corneal decompensation but also to plan and monitor the effects of surgery.

Specular endothelial photomicroscopy has demonstrated that age is a poor predictor of ECD[9-13] and that corneal thickness, though a useful measure of endothelial function, is a poor predictor of cell density.[2,14] Other signs of endothelial abnormality include the presence of guttae or an increase in the cellular pleomorphism[14,15]; both of these changes tend to be associated with lower ECD. Illustrations of the corneal endothelial mosaic in health and disease, as demonstrated on the Gullstrand slit-lamp, have been published by Vogt.[16] Although the matching of slit-lamp visualisation of the mosaic to a series of standardised grids or a graticule has been described,[17-20] there has been no report of a comparison between the ease of slit-lamp visualisation of the mosaic and the ECD measured by specular photomicroscopy.

This paper reports a study of the validity of a clinical assessment of corneal endothelial cell density, considers theoretical aspects, and derives guidelines for clinical management. The aims of this study were (*a*) to increase the clinical awareness of the facility of slit-lamp specular illumination and thereby to increase its practice; (*b*) to provide a method of conveniently recording approximate cell densities for clinical practice and for future reference by the same observer; and (*c*) to highlight the fact that low endothelial cell densities, of particular concern surgically, are readily recognisable at the slit-lamp microscope.

Materials and Methods

The corneas of 236 subjects were examined by the writer on two occasions, these examinations being separated by at least 10 weeks and the second being without reference to the results of the first; the work was completed within one year. Subjects on long-term eye medication were omitted from the study.

At each examination the ease of visualisation of

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the endothelial mosaic was graded by means of a Haag-Streit 900 slit-lamp microscope (by a technique detailed later), the density of corneal guttae was assessed (subjective scale, range 0–5), the degree of corneal arcus was graded (subjective scale, range 0–3), and the presence of stromal opacity or disease was noted. The central corneal thickness was measured with a Haag-Streit pachymeter (mode of three or more readings, with avoidance of instrument 'backlash' errors). After the clinical assessment of a cornea, specular photomicrographs of the central corneal endothelium were made with a Pocklington contact specular microscope (Keeler–Konan).

ECD was assessed by the projection of the photomicrographs to a known magnification and by counting of the number of cells in an area of known size.[21] The system was calibrated by the use of a haemocytometer, allowance being made for a corneal thickness of 0·55 mm. Made by a single independent observer, the number of counts for each examination was normally three or more (range 1–6).

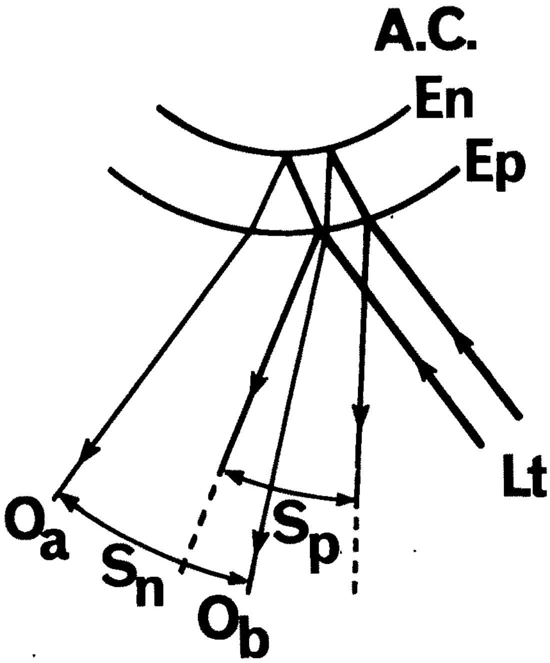

Fig. 1 *Ray diagram of the specular corneal reflections produced by a collimated light source* (Lt); *only extreme rays are represented. The endothelium* (En) *with low reflectance, produces a zone of low-intensity specular endothelial reflection* (S_n), *this zone often being overlapped by a high-intensity specular reflection* (S_p) *from the epithelium. The degree of overlap is dependent on illumination beam width, corneal thickness (and refractive index), and the angle between the light-source beam and the observer. Observation at position* O_a *would provide an endothelial image of optimum quality, whereas that at* O_b *would be saturated by light reflected from the epithelium.* A.C. *denotes anterior chamber.*

PRACTICE OF SPECULAR ILLUMINATION

To visualise the low-reflectance corneal endothelial mosaic without the image being saturated by extraneous light from the high-reflectance epithelium requires considerable practice. The fundamental basis of the technique, namely *specular* (as opposed to diffuse) reflection of light, dictates that, on a convex reflecting surface (such as the cornea), there is, for a given position of light source and observer, only a *single point* that will produce a specular reflection. The practical implication is that the area illuminated should be kept as small as possible to reduce extraneous reflected light; a slit-beam 0·5×2 mm is in general adequate. An additional restriction, again dictated by this 'three-point' optical model, is that the specular reflection can be viewed only monocularly. Although the use of a second ocular (as available on the slit-lamp microscope) can provide a slightly larger field of view, one or both of the images must by definition be suboptimal. Furthermore with wider beams of incident light the low reflectance endothelial image is increasingly spoilt by light from the high reflectance epithelial surface (Fig. 1).

In this study the following technique was developed, based on the reasons detailed:

It is imperative to adjust the eyepieces on the

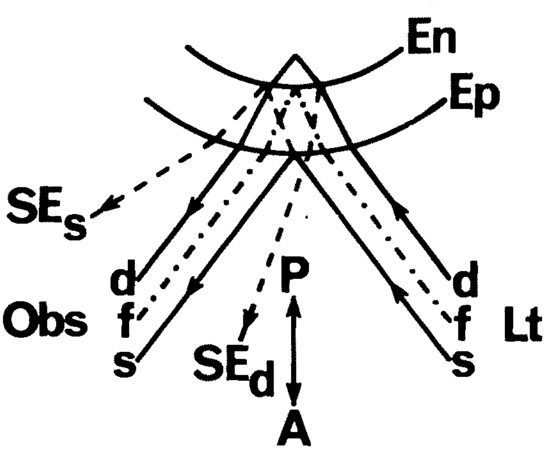

Fig. 2 *Effect of adjustment of the slit-lamp microscope, along the anteroposterior* (AP) *axis, on the specular endothelial reflection; ray diagram illustrating only single rays, passing from the light source* (Lt) *to the observer* (Obs). *When focused deeply* (d-d) *to the ideal position* (f-f), *the specular endothelial reflection bypasses the observer to reach* SE_d; *when focused superficially* (s-s), *the reflection bypasses the observer to* SE_s. A.C. *denotes anterior chamber.*

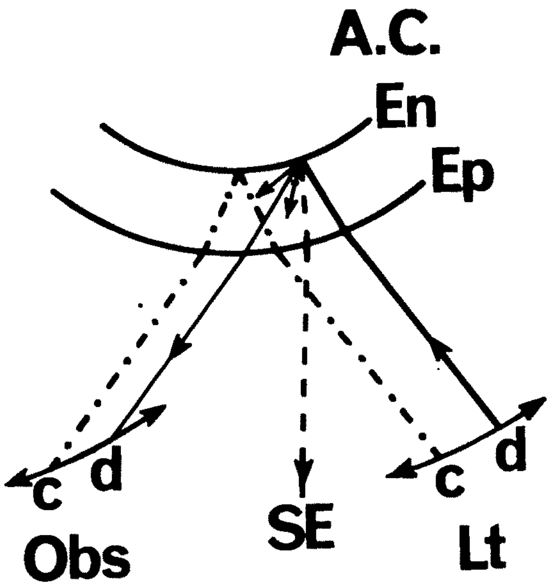

Fig. 3 *Effect of adjustment of the slit-lamp microscope, along a line* (cd) *parallel to the plane of the corneal endothelial surface; ray diagram illustrating only single rays from light source* (Lt) *to observer* (Obs). *When displaced* (d-d) *from the ideal position* (c-c), *the specular reflection from the endothelium bypasses the observer to reach* SE. *The image of the endothelium viewed by the observer at position* d *is that due to diffuse (non-specular) reflection at the endothelial surface (thin and short arrows).* A.C. *denotes anterior chamber.*

slit-lamp microscope to observer emmetropia. Ametropic settings, frequently found, contribute to a poor visualisation.

With the illumination beam locked at 20°–30° to the microscope boom, the endothelial reflection is focused in the anteroposterior axis (AP axis; AP on Fig. 2). If the focused deep to the endothelium, the specular image bypasses the observer (Obs) on the side of the illumination and vice versa (Fig. 2). In practice one maximises the intensity of reflected light by altering the AP position and brings into focus the mosaic if visible.

If the instrument AP axis does not correspond with the anteroposterior axis of the convex corneal surface (Fig. 3), then the specular reflection will again bypass the observer (Obs) even though, viewed by diffuse illumination, the endothelial mosaic might be in focus. To remedy this situation the slit-lamp mounting must be moved in an arc paralleling the corneal convexity (line cd; Fig. 3), until maximum specular reflectance of a focused endothelial image is achieved.

GRADING OF ENDOTHELIAL VISUALISATION

By means of this method the appearance of the mosaic was graded thus:

Grade 0: Mosaic not visible at high-power objective setting on the slit-lamp (×16).
Grade 1: Mosaic barely visible ('grainy' image) at ×16.
Grade 2: Mosaic visible at ×16 after >15 seconds.
Grade 3: Mosaic readily visible at ×16, within seconds, but not visible at low-power setting (×10).
Grade 4: Mosaic barely visible ('grainy' image) at ×10.
Grade 5: Mosaic visible at ×10, after >15 seconds.
Grade 6: Mosaic readily visible at ×10, within seconds.

ANALYSIS

By the use of generalised linear models which incorporate the statistical techniques of multiple regression and analysis of variance,[22] it was possible to determine the relation between the factors assessed clinically and the ECD derived from specular photomicrography.

The first group (group I) consisted of single eyes from 122 subjects, these eyes being unoperated upon. In all cases the right eye was chosen unless either the right eye had been previously operated upon or the subject's left eye was to undergo cataract extraction.

In the second group (group II) single eyes from 192 subjects were examined between 10 and 30 weeks after cataract extraction, with or without lens implantation. Seventy-six of these postoperative eyes were also examined preoperatively in group I.

In the third group (group III) were 53 eyes not operated upon. These eyes were twice assessed, in a masked manner, at between 10 and 30 weeks.

Results

The groups were well matched with respect to age: group I, 68·7±12·7 years (mean±standard deviation); group II 69·8±11·2 years; and group III 68·2±11·7 years. Similarly, they were matched for the proportion of diabetics (group I 10%, group II 10%, and group III 8%). The number of subjects within each of the visual gradings is summarised in Table 1.

Both in group I and in group II visual grading proved to be statistically a very highly significant predictor of cell density (F test; $p \ll 0{\cdot}001$ for both groups). Within the preoperative group (group I), the presence of stromal opacity or disease proved also to be a significant additional predictive factor ($p < 0{\cdot}01$), while in the postoperative group (group II), the grading of guttae appeared to be a weak, but sig-

Table 1 *Mean cell density for each clinical grading (with standard error of mean (SEM) and the number of values) within group I (preoperative) corneas, group II (post-operative) corneas, and within the combined groups I and II. Endothelial cell densities expressed as cells/mm²*

Group		*Visual grading of corneal endothelium*							*Total*
		0	*1*	*2*	*3*	*4*	*5*	*6*	
Pre-	Mean	2553	2289	2106	1861	642	—	—	
operative	SEM	60	40	61	220	—	—	—	
(Group I)	Number	28	53	34	6	1	0	0	122
Post-	Mean	2204	2225	1948	1694	1226	614	552	
operative	SEM	79	46	58	75	123	.56	—	
(Group II)	Number	22	74	63	22	8	2	1	192
Combined	Mean	2400	2252	2003	1730	1161	614	552	
(Groups	SEM	54	32	44	74	126	56	—	
(I&II)	Number	50	127	97	28	9	2	1	314

nificant, additional factor ($p<0{\cdot}05$). In neither group was there a significant relation between ECD and the age of the subject, a history of previous eye disease or of diabetes, the degree of corneal arcus, or the central corneal thickness. Moreover within group II subjects the implantation of an intraocular lens was not a significant factor in predicting ECD after the significance of the visual grading was taken into account.

VISUAL GRADING

The mean ECD within each of the clinical visual gradings is represented in Fig. 4. As reasonably expected, the ease of visualisation (grading scale) increases as the ECD decreases (cell size increases). The similarity between the gradings of the preoperative and the postoperative eyes is notable. In addition the observation that the mean ECDs in grades 0–3 are consistently lower in the postoperative compared with the preoperative corneas suggests that some postoperative factor—perhaps, for example, minimal corneal oedema or irregularities in Descemet's membrane—is acting to reduce slightly the visibility of the corneal endothelial mosaic (but not to a statistically significant degree).

REPRODUCIBILITY

In the 53 corneas tested for intraobserver variation (group III) there was no significant change in corneal thickness measurements; the mean difference between initial and repeated measurements was 0·0038 mm (initially larger; standard deviation of difference=0·0065, $p>0{\cdot}3$). Similarly, the mean difference between ECDs (18 cells/mm², initially larger) was not significant (SD difference=64, $p>0{\cdot}5$).

Table 2 *Reproducibility of the grading of 53 corneas. The number within each combination of initial and repeated grading is indicated; values on the line of identity are underlined*

Initial visual grading	*Repeated visual grading*			
	0	*1*	*2*	*3*
0	4	6	1	0
1	1	20	3	2
2	0	5	8	1
3	0	0	1	1

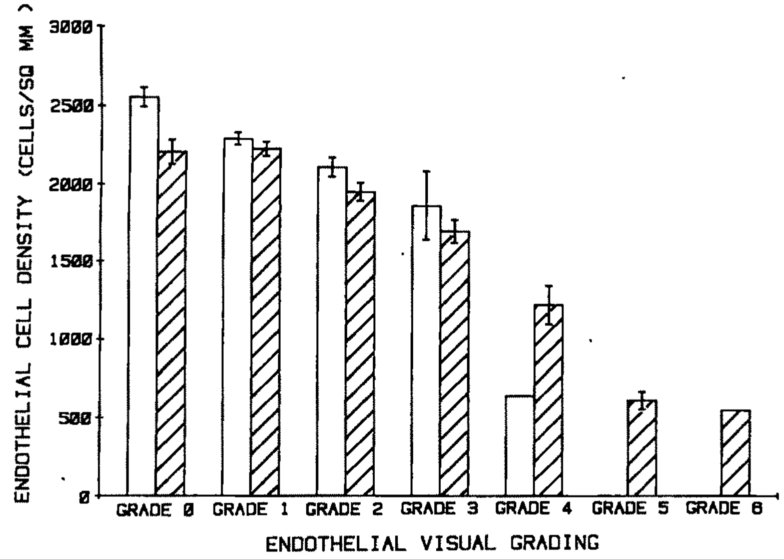

Fig. 4 *Mean endothelial cell densities for each visual grading of preoperative corneas (open bars) and postoperative corneas (cross-hatched bars); error bars represent mean ± one standard error. Number of corneas in each group is summarised in Table 1.*

Table 3 *Percentage probabilities that a cornea of known endothelial visual grading would lie within each of four endothelial cell density ranges (see text for example); cell densities expressed as cells/mm^2. With the exception of grade 6, for each visual grading the probabilities within each grade are calculated from estimates of the mean and standard deviation for that grade (values in Table 1) and the distribution of the Student's t statistic; estimates were derived from a 'pooling' of group I and group II corneas (total number=314). The estimates for grade 6 were derived from a pooled estimate of standard deviation and the distribution of the z statistic*

Range of cell density	*Visual grading of corneal endothelium*							*Surgical comment*
	0	*1*	*2*	*3*	*4*	*5*	*(6)*	
>1500	>99%	98%	88%	72%	20%	3%	(>1%)	'Safe.' Unlikely to decompensate, even after major surgery
1500–1000	<1%	2%	11%	24%	46%	4%	(11%)	'Safe' for majority of surgery. 'At risk' for procedures with major or continued cell loss
999–500	0%	0%	1%	3%	28%	73%	(39%)	'At risk' for majority of surgery and major procedures likely to decompensate cornea
<500	0%	0%	0%	<1%	6%	20%	(49%)	Corneal decompensation inevitable

There was, however, some variation on repeated visual grading of the corneas (Table 2). Most notable is the slight tendency towards increased visualisation (higher grading) on repeating the assessment. Thirty-three corneas had the same initial and repeated grading, more than the 20 agreements expected by chance alone.

Discussion

It has been demonstrated that the corneal endothelial mosaic can usefully be graded, albeit with some variability, and that this grading is closely related to the central corneal ECD as determined by specular photomicrography. This fast method requires neither special grids or graticules nor the processing and time-consuming assessment of specular photomicrographs. However, the grading not only requires the observer to have a normal visual acuity, but also can be difficult in the presence of stromal opacity or of small eye movements. Indeed, the author considers it to be a wise precaution in clinical practice to increase a grading by one category in the presence of persistent small eye movements.

The grading is subject, without doubt, not only to variability when used by one observer (visualisation improves markedly with practice of specular illumination), but also to considerable variation between observers. Because of this the grading is *not* intended as a substitute for the objective record of photomicroscopy, but rather as an encouragement for the neglected clinical art of specular illumination, as a method of recording approximate ECDs prior to surgery and as a means of assessing endothelial losses when repeated measurements are made by any one observer.

VISUAL ACUITY AND THE LIMIT OF CELL RESOLUTION

By calculating the angular visual resolution required to see those cells at the limit of slit-lamp resolution (i.e., those cells in grade 1), this calculated angular resolution is found to be in close agreement with the generally accepted optical resolution of the healthy eye. This calculation, demonstrating concordance between observation and theory, is presented in Appendix I.

CLINICAL USAGE OF THE GRADING SYSTEM

Not only does the system of grading provide an indication of the mean ECD in both preoperative and postoperative corneas (Fig. 4), but also the deductions may be extended to provide a guide more useful in clinical practice (Table 3).

From the mean cell density and variance estimates from the combined results of groups I and II (Table 1), for each visual grading the probability of a subject lying within one of four surgically relevant ECD ranges (>1500, 1500–1000, 999–500, and <500 cells/mm^2) can be estimated (Table 3). Thus, if a patient has a clinical grade 4 corneal endothelium, he has (based on the present series) a 20% probability of having a cell density of greater than 1500 (and tolerating major anterior segment surgery), a 46% chance of having a density of 1000–1500 (where major surgery may jeopardise the corneal compensation), a 28% chance of having a cell density of 500–1000 (where corneal decompensation becomes likely after surgery), and a 6% probability of having a cell density below 500 cells/mm^2.

In clinical practice these 'risk' factors can be weighed against the necessity of the surgery and the life expectancy of the patient.

Appendix I

From the mean ECD of grade 1 visualisations a grading at the limits of resolution at 16-fold magnification—

D, the mean ECD (pooled estimate group I and group II, $n=127$) is given by:

$$D = 2250 \text{ cells/mm}^2;$$

A, the mean cell area is thus given by:*

$$A = 1/D$$
$$= 4{\cdot}4 \times 10^{-4} \text{ mm}^2.$$

If the shape of the cells is taken to be circular, then diameter, d, is given by:

$$d = 2\sqrt{A/\pi}$$
$$= 2{\cdot}4 \times 10^{-2} \text{ mm}.$$

At the usual slit-lamp microscope image distance of 250 mm, the angle G subtended in the vertical meridian* by such a cell, unmagnified, is given by:

$$G = d/250$$
$$= 9{\cdot}5 \times 10^{-5} \text{ radians}$$

But, with ×16 (high-power) magnification, the image subtends an angle, G′, given by:

$$G' = 16 \times G$$
$$= 1{\cdot}5 \times 10^{-3} \text{ radians}.$$

However, the limit of resolution is set by the width of the cell boundaries as contrasted on specular illumination. From analysis of specular micrographs the cell boundary width is found to be between approximately one-seventh and one-tenth of the cell 'diameters' (personal observation).

Thus the angular visual acuity, V, required to resolve the endothelial mosaic under the defined conditions is given by:

$$\text{Range of } V = G'/7 \text{ to } G'/10$$
$$= 2{\cdot}2 \times 10^{-4} \text{ to } 1{\cdot}5 \times 10^{-4} \text{ radians}$$
$$= 0{\cdot}75' \text{ to } 0{\cdot}5' \text{ arc}.$$

This calculated angular visual resolution (0·5′–0·75′) is of the same order of magnitude as that generally accepted to be the optical resolution of the healthy eye.

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* The obliquity of slit-lamp microscope specular illumination results in a small reduction in image sizes in the horizontal meridian. This 'scaling factor' approximates to the cosine of A/2, where A is the angle subtended by the illumination and the observer axes at the corneal surface. In practice this factor varies between the negligible values of 0·98 and 0·96 if specular illumination is practised as detailed.

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Iris atrophy in sickle cell disease

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SUMMARY Iris atrophy, of unknown origin and believed to be secondary to the vaso-occlusive process of sickle cell disease, has been observed in 25 eyes of 22 patients (two SS disease, 20 SC disease). The crude prevalence was highest in males with SC disease, in whom 14·7% of patients were affected. Iris atrophy was closely associated with proliferative sickle retinopathy in the same eye. Analysis of haematological indices failed to reveal any significant differences between patients with and without iris atrophy. The characteristics and distribution of iris atrophy are described as well as the histopathology in one 68-year-old male patient with SS disease.

The vaso-occlusive process characteristic of sickle cell disease produces a variety of lesions in the eye. Although most widely recognised in the conjunctival vessel anomalies and in ischaemia of the retinal periphery with proliferative sickle retinopathy, the iris vessel system may also be affected. Iris atrophy has been previously reported in six eyes of three patients, all with sickle cell-haemoglobin C (SC) disease,[1 2] but no assessments of prevalence have been possible. The screening of large numbers of patients with sickle cell disease in Jamaica has detected 26 patients with iris atrophy, allowing an assessment of the prevalence, risk factors, associated clinical features, and characteristics of this complication.

Material and methods

The patients attended the Sickle Cell Clinic of the University Hospital of the West Indies, Kingston, Jamaica, and a group of peripheral sickle cell clinics operated by the staff of the Medical Research Council (MRC) Laboratories. During the period 1 January 1984 to 31 May 1985 examination of the iris was performed in 414 patients aged 15 years and over. There were 182 patients (75 male, 107 female) with homozygous sickle cell (SS) disease and 232 patients, (116 male, 116 female) with sickle cell-haemoglobin C (SC) disease. Phthisis bulbi precluded observations on one eye of six patients (one SS male, five SC males), but the iris was examined in the remaining 822 eyes of 414 patients. All patients with iris atrophy had detailed examinations of the anterior chamber with slit-lamp, gonioscopy, photography and tonometry, and fundus examinations. Fluorescein angiography of the iris was performed in selected cases.

The extent of sectoral iris atrophy was measured circumferentially by clock hours and radially with the collarette and contraction furrows as landmarks. Non-sectoral atrophic patches in the iris were measured as diameter in millimetres. Histological examination of iris atrophy was possible in one patient who died during the course of the study.

Results

Iris atrophy was present in 31 eyes of 26 patients. In two eyes (both SC females), the iris atrophy occurred as part of the syndrome of anterior segment ischaemia, and in one SS female patient an atypical sectoral iris atrophy was noted in an eye which had previously been operated on for detached retina. In three eyes (one SS male, two SC males), a history of trauma and notching of the pupil with or without angle recession suggested that trauma may have been causally related to the iris atrophy. There remained a group of 25 eyes in 22 patients in whom the likely cause of iris atrophy was a sickle cell related occlusion of the vascular supply of the iris ('spontaneous' iris atrophy).

In this spontaneous group there were two patients with SS disease (one male, one female) and 20 patients with SC disease (17 male, three female).

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Table 1 *Crude prevalence rates of 'spontaneous' iris atrophy*

	Patients		*Eyes*	
	Total examined	*Total affected*	*Total examined**	*Total affected*
SS disease				
Males	75	1 (1·3%)	148	1 (0·7%)
Females	107	1 (0·9%)	213	1 (0·5%)
SC disease				
Males	116	17 (14·7%)	225	20 (8·9%)
Females	116	3 (2·6%)	230	3 (1·3%)

*Excluding those with phthisis bulbi and those with iris atrophy probably associated with anterior segment ischaemia or trauma.

Table 2 *Age of patients affected by 'spontaneous' iris atrophy*

Age group (years)	*SS disease*		*SC disease*	
	Patients		*Patients*	
	Examined	*Affected (%)*	*Examined*	*Affected (%)*
15–29	87	0 (—)	136	2 (1·5)
30–44	69	0 (—)	70	13 (18·6)
45+	26	2 (7·7)	26	5 (19·2)

The crude prevalence rates (Table 1) confirm the complication to be most common in males with SC disease. The age of onset was unknown, since in none of the 'spontaneous' cases was the onset of iris atrophy prospectively recorded, but the complication appeared to be more common with advancing age (Table 2).

Iris atrophy affected the right eye in 12 patients, the left in seven, and was bilateral in three (all SC males), the difference in right/left distribution failing to reach significance at the 5% level. The pattern of iris atrophy was confined to sectoral involvement limited to the pupillary margin in two eyes (type 1), extending radially from the pupillary margin to the collarette (type 2) in nine eyes, and to the contraction furrows (type 3) in nine eyes. Atrophy was confined to circumscribed areas measuring 1–4 mm diameter in the ciliary zone in four eyes. One patient had both a type 3 radial involvement from 9 to 1 o'clock and a separate lesion in the ciliary zone at 5 o'clock (Fig. 1). The extent of circumferential involvement by sectoral lesions varied from 30° to 180° with a median of 90°. The 21 sectoral lesions affected predominantly the temporal side in 16 eyes and the nasal side in five eyes, the difference being significant at the 5% level. Of the five ciliary lesions four occurred in nasal sectors and one at 6 o'clock.

Atrophic areas appeared thinned and flat with loss of the normal folds of stromal tissue (Fig. 2), and appeared to affect predominantly the anterior border layer and stromal tissue. In sectoral lesions the pupillary margin was always affected, with loss of the normal pupillary frill and occasionally rupture of the pupillary margin (Fig. 3). When retroilluminated the

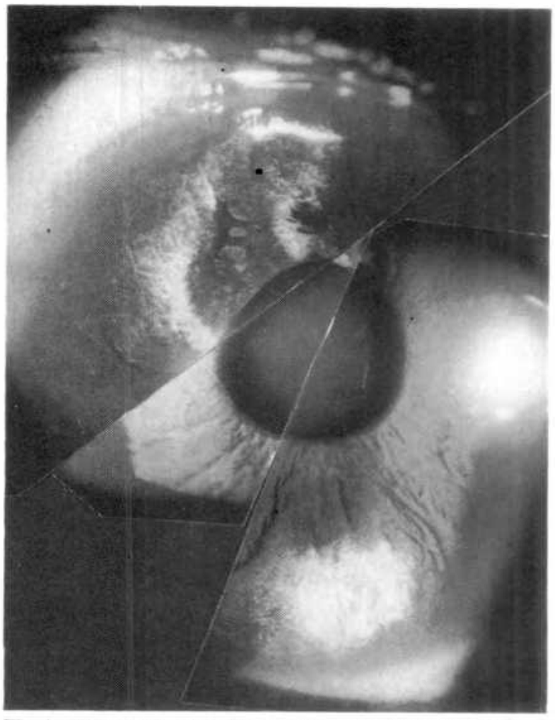

Fig. 1 *Composite photograph of iris atrophy in the right eye of a 43-year-old male with SC disease demonstrating both sectoral iris atrophy at 9 to 1 o'clock and a circumscribed area in the ciliary zone at 5 o'clock.*

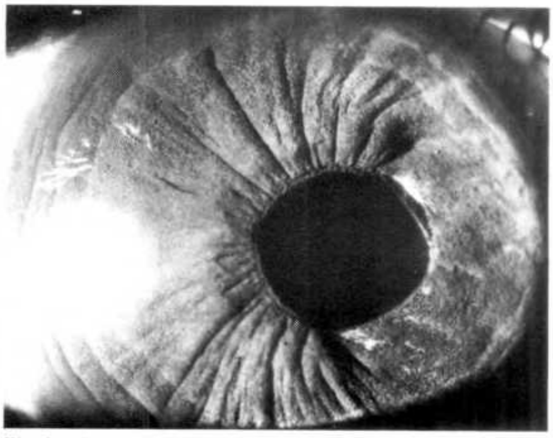

Fig. 2 *Sectoral iris atrophy from 1 to 6 o'clock in the nasal side of the right eye in a 25-year-old male with SC disease.*

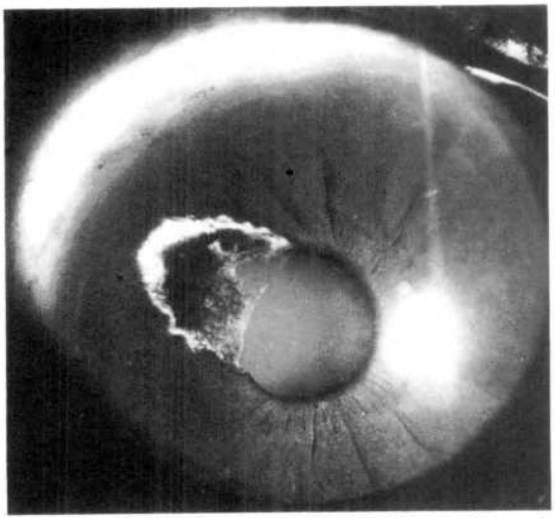

Fig. 3 *Sectoral iris atrophy from 8 to 12 o'clock in the nasal side of the left eye in a 46-year-old female with SS disease.*

atrophic areas could be seen to be thin and translucent with full thickness holes. Pigmentary changes were common in atrophic areas, hyperpigmentation occurring occasionally but most areas being mottled with pale white fibres coursing radially (Fig. 4). The atrophy never extended peripheral to the contraction furrows, and the anterior chamber angles were normal and open, though eyes with iris atrophy frequently showed more pigment, especially in the inferior angle, when compared with eyes without iris atrophy. Sphincter function was affected in some patients.

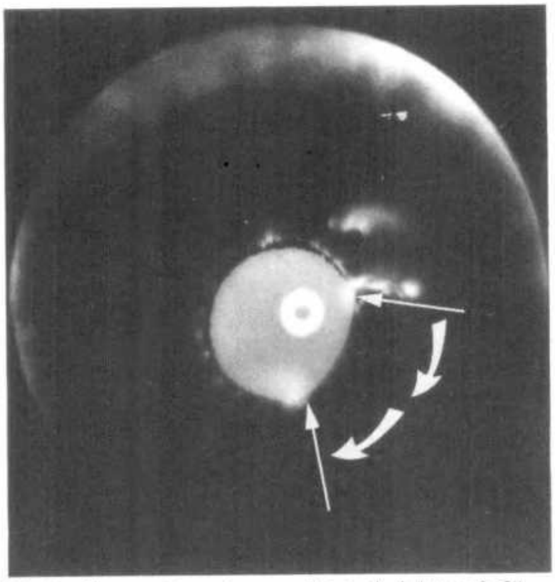

Fig. 5 *Fluorescein angiogram of iris in the left eye of a 59-year-old male with SC disease. White arrows mark extent of sectoral iris atrophy.*

Fluorescein angiography of the iris in nine eyes (seven patients) confirmed that the atrophic areas were avascular. Leakage of fluorescein was generally confined to the margin of the atrophic areas (Fig. 5), but occasionally a spotty leakage was observed over the whole surface of the iris (Fig. 6).

The histopathology of iris atrophy was studied in a 68-year-old male with SS disease in whom a sectoral

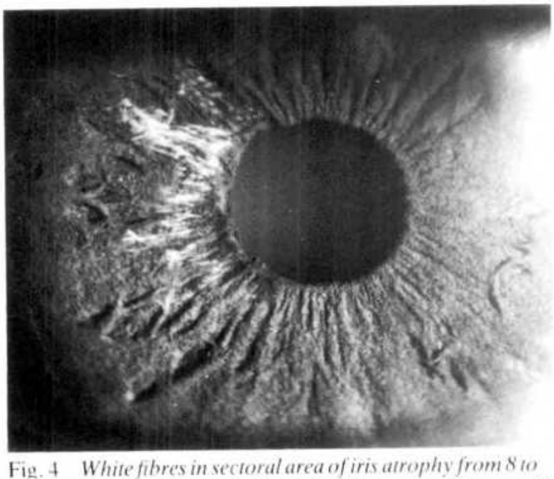

Fig. 4 *White fibres in sectoral area of iris atrophy from 8 to 11 o'clock in the temporal side of the right eye in a 56-year-old female with SC disease.*

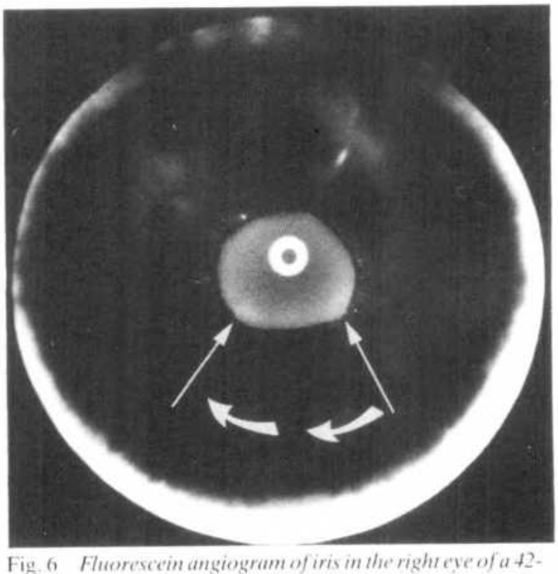

Fig. 6 *Fluorescein angiogram of iris in the right eye of a 42-year-old male with SC disease showing diffuse spotty leakage. White arrows mark the extent of sectoral iris atrophy.*

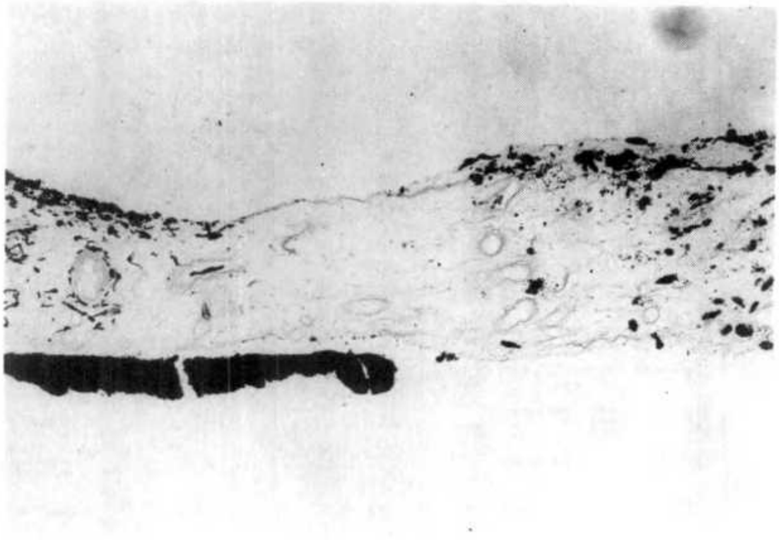

Fig. 7 *Section through full-thickness infarct of iris stroma in a 68-year-old male with SS disease. The detachment of pigment epithelial layer to the right side of the figure was artefactual. (Haematoxylin and eosin, ×50).*

necrosis from 9 to 12 o'clock extended from the pupillary margin to the contraction furrows of the right eye. Pathological examination showed necrosis between the midzone of the iris and the pupillary margin, generally affecting the anterior part of the stroma, though there was a full-thickness infarction of the iris at one site (Fig. 7). The dilator and sphincter pupillary muscles were involved by infarction and atrophy was visible adjacent to the infarcted area. Areas of infarction were seen at the root of the iris. The pigment epithelium was generally intact and appeared to be spared by the infarctive process, but pigment from necrotic melanocytes in the stroma was dispersed and removed from infarcts at later stages. There was focal ischaemic necrosis and atrophy with coagulative necrosis of blood vessels and stroma. Endothelial cell nuclei failed to stain, leaving ghosts of blood vessels amid dissociated wisps of stromal fibres. Blood vessels in the ciliary body contained sickled red blood cells, but there was no evidence of organised thrombus, vessel wall thickening, or of an active inflammatory process.

The preponderance of iris atrophy among SC males raises the possibility of an association with proliferative sickle retinopathy (PSR), which is also recognised to be most common in this group. This analysis was confined to male SC patients in whom 212 eyes were observed for both iris atrophy and PSR. Iris atrophy occurred in 19% of eyes affected by PSR but was observed in only 2% of eyes without PSR (Table 3), the difference being highly significant. Of the 20 eyes with iris atrophy 18 had PSR in the same eye and two had PSR in neither eye. Since many of the patients with PSR had received photocoagulation therapy with either the xenon arc or argon laser, it was possible that the high prevalence of iris atrophy in PSR patients was related to therapy. Further analysis of the prevalence of iris atrophy in those with PSR with photocoagulation (18% iris atrophy) and without photocoagulation (20%) revealed no difference between the groups (Mantel-Haenszel $\chi^2=0{\cdot}003$, not significant) indicating that photocoagulation did not appear to increase the chance of developing iris atrophy.

A study of the haematological risk factors for iris atrophy was performed by comparing by Student's *t* test the distribution of haematological indices in those with and without iris atrophy. In order to minimise sex and age related differences this study was confined to male patients with SC disease aged 30 years and over and utilised the most recent steady state data for each patient (mean 2·2 years earlier, range 0-7 years). The results (Table 4) indicate that

Table 3 *Prevalence of iris atrophy in SC male eyes with and without PSR*

Age group	*PSR positive*			*PSR negative*		
	Iris atrophy			*Iris atrophy*		
	+	−	*% +ve*	+	−	*% +ve*
15–29	2	36	5	0	86	0
30–44	12	31	28	2	22	8
45+	4	10	29	0	7	0
All	18	77	19	2	115	2

Mantel-Haenszel χ^2 allowing for age groups $=7{\cdot}29$, $p<0{\cdot}01$.

Table 4 *Some haematological indices in male SC patients with and without iris atrophy*

	Iris atrophy (n=15)		*No iris atrophy (n=34)*		*Significance t*	
	Mean	*SD*	*Mean*	*SD*		
Log (HbF+4)	1·56	0·14	1·62	0·17	−1·14	NS
Hb	13·3	1·3	12·7	1·3	1·58	NS
MCHC	35·7	1·7	35·6	1·9	0·18	NS
MCV	88·6	7·1	84·3	7·2	1·93	NS
Log (reticulocytes+1)	1·67	0·36	1·41	0·47	1·94	NS

NS=not significant at the 5% level.
MCHC=mean corpuscular haemoglobin concentration.
MCV=mean cell volume.

patients with iris atrophy tended to have lower levels of fetal haemoglobin and higher values for mean cell volume (MCV) and reticulocyte count, but none of the differences were significant at the 5% level. In view of the strong relationship between iris atrophy and PSR, and of the previously established relationship of PSR with higher MCV and lower HbF, the lack of significant relationships with iris atrophy was surprising but probably simply reflected the small size of the study group.

Discussion

Iris atrophy has been previously reported in only three patients with sickle cell disease,[1 2] giving the impression that this is an uncommon finding. The current report describing 31 affected eyes indicates that it is relatively common. Some of these cases have well recognised causes such as anterior segment ischaemia; involvement of a single eye in a female with SS disease was excluded from the series, since it may have been secondary to retinal detachment surgery. Trauma is also a well documented cause, and three further cases were excluded as being possibly attributable to this. All had a history of moderate trauma, all had notching of the pupil one showed mild angle recession, but none had evidence of radial splits or iridodialysis. None of the remaining cases had evidence of other known causes such as quinine[3] or herpes zoster,[4] and there remained a group of 25 eyes in 22 patients who were presumed to have 'spontaneous' iris atrophy associated with sickle cell disease.

This finding is reported for the first time in two patients with SS disease but is most common in male patients with SC disease, occurring in nearly 15% of this group. This prevalence is probably broadly representative of the patients at risk, though may be affected by a variety of selection biases. Since vaso-occlusion is believed to occur more frequently in SS disease, the greater prevalence of iris atrophy in SC disease is an unexpected finding. It is known that PSR occurs much more frequently in SC disease, but this was believed to be because the greater vaso-occlusive tendency in patients with SS disease occluded the abnormal vessel systems that preceeded PSR, thus inhibiting its development. It would be difficult to envisage how such a mechanism could contribute to the high prevalence of iris atrophy in SC disease.

The highly significant association between iris atrophy and PSR in the same eye imples that, if clinical examination detects iris atrophy, there is a 90% chance of PSR occurring in the same eye. This association also suggests that there may be common risk factors for the two complications. However, analysis of certain haematological indices known to be significantly associated with PSR in SC disease[5] failed to show significant differences between cases with and without iris atrophy, though there were similar trends, and the lack of significance may have simply reflected the small numbers available for analysis.

The mechanism of vaso-occlusion in the iris is not understood. Although macroscopically the infarcted areas did not appear to extend peripheral to the contraction furrows, the histopathology in the one examined case showed areas of necrosis extending to the root of the iris. The blood supply of the iris is derived from a greater arterial circle in the root of the iris, radial vessels coursing towards the pupillary margin, and a minor arterial circle at the level of the collarette. The area between the collarette and the pupillary margin has the greatest density of fine vessels, and yet this is the region most frequently affected by infarction. Studies of iris circulation by fluorescein angiography in patients with blue irides[6] have indicated that iris vessels fill more slowly than those in the retina or choroid and that the central part of the iris fills much more slowly than the root, the nasal vessels filling before the temporal vessels. These observations are compatible with the observed pattern of iris atrophy in these patients, which affected predominantly the pupillary margin and central areas, and the temporal side more frequently than the nasal. Unfortunately fluorescein angiography in patients with brown irides is much less informative because of pigment in the iris stroma, and only poor vessel detail is available. A patient studied by Galinos *et al.*[1] had a peripupillary neovascular network and a vascular formation resembling a sea fan, though the patient also had diabetes mellitus, suggesting an alternative aetiology for these changes. In the present study fluorescein angiography of the iris in nine eyes revealed almost no vessel details, though atrophic areas appeared to be avascular, and spotty leakage of dye from clinically unaffected areas suggested a more widespread vessel abnormality.

Much remains to be learnt about the factors contributing to iris atrophy in sickle cell disease. Although this complication is of limited functional significance, the mechanisms involved may be instructive for the understanding of vaso-occlusion elsewhere in sickle cell disease.

We thank Mr R J Marsh, FRCS, of the Western Ophthalmic Hospital, London and Mr T A Gardiner, MSc, of the Department of Ophthalmology, Queen's University of Belfast, for valuable discussion.

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Blood rheology and proliferative retinopathy in homozygous sickle cell disease

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SUMMARY Some haematological and rheological features were compared in 27 age and sex matched pairs of patients (15 male, 12 female) with homozygous sickle cell (SS) disease with and without proliferative sickle retinopathy (PSR). Significant haematological differences between the groups were a higher haemoglobin and a lower fetal haemoglobin in PSR positive males and a higher MCHC in PSR positive females. The plasma viscosity and characteristics of erythrocyte filterability did not differ between those with and those without PSR, although PSR positive males had a significantly higher whole blood viscosity when measured at high shear and at the patient's own packed cell volume.

Although proliferative sickle retinopathy (PSR) is accepted as a sequel to vaso-occlusion in the peripheral retina in homozygous sickle cell (SS) disease, the factors which render only a minority of patients prone to this condition are largely unknown. An analysis of haematological differences between patients with SS disease with and without PSR[1] indicated that patients with a combination of high haemoglobin levels and low fetal haemoglobin (HbF) levels were at greatest risk. Age is also important, the frequency of PSR rising with age after 10 years and the complication being especially prone to develop between the ages of 15 and 29 years.[2] A further factor complicating the assessment of risk factors for PSR is the frequency of autoinfarction, which may abort the pathological process of PSR.[3]

Since important risk factors for PSR must reside in the haematological abnormalities of patients with SS disease, some characteristics of blood viscosity and of erythrocyte deformability have been studied in age and sex matched groups of patients with and without PSR.

Materials and methods

The patients were drawn from the Sickle Cell Clinic of the University Hospital of the West Indies and from a group of peripheral sickle cell clinics all operated by the staff of the Medical Research Council (MRC) Laboratories. There were 27 patients (15 male) with PSR who were each matched with a patient of the same sex and similar age in whom retinal examination within the last year had confirmed the absence of PSR. Where possible the viscosity studies were performed on patients and controls on the same day. Ages ranged from 21 to 54 years (patients) and from 21 to 56 years (controls), with a mean age of 37·2 years in the PSR group and 38·1 years in the controls. Since homozygous α thalassaemia 2 is known to influence blood rheology,[4] patients with this genetic subdivision of SS disease were avoided in all but one female index case.

The criteria for the diagnosis of SS disease[5] and the techniques of ocular examination[6] were as previously described. Plasma fibrinogen was measured by the clot weight method.[7] Blood viscosity was measured at 25°C and high ($230 s^{-1}$) shear rate in a Wells-Brookfield microviscometer and plasma viscosity at 25°C in a Coulter-Harkness capillary viscometer, as decribed elsewhere.[4] Each patient's blood was adjusted by removing or adding plasma to give three samples of different packed cell volume (range 0·30–0·40). A regression line of log viscosity against packed cell volume (PCV) for the three samples was drawn, so that viscosity values corresponding to the patient's original PCV and to a standard value of 0·45 could be calculated.[4] Erythrocyte deformability (filterability)

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was measured at ambient temperature by a positive pressure, constant flow system using 5 μm pore diameter polycarbonate membranes (Nucleopore Corporation, Pleasanton, USA), as previously described.[4] The characteristics of the time-pressure curves were analysed[8] into four components, the initial pressure (Pi), the final pressure (Pf), the initial steep slope (slope 1) representing the rise in pressure as the erythrocytes encountered the filter and a second more gradual slope (slope 2) representing the increment in pressure necessary to maintain filtration. All four parameters were strongly correlated and, as previously,[8] Pi and slope 2 were arbitrarily selected to define the characteristics of the curve.

Statistical analysis was by Student's t test for matched pairs and by multiple logistic regression.[9] Variables with skewed distributions (reticulocytes, HbF, fibrinogen, and slope 2) were transformed as follows: $\log_e$ (reticulocytes+1), $\log_e$ (HbF+1), $\log_e$ (fibrinogen), and $\log_e$ (slope 2+1) to provide approximately normal distributions.

Results

Some haematological features in the PSR and non-PSR groups are presented for male and female patients in Tables 1 and 2 respectively. Male patients with PSR had significantly lower HbF and significantly higher haemoglobin and packed cell volume than males without PSR, as previously noted.[1] No such difference was apparent in female patients, though a significantly higher mean corpuscular haemoglobin concentration (MCHC) occurred in the PSR group.

The viscosity and erythrocyte filterability results for the two sexes are summarised in Tables 3 and 4 respectively. Whole blood viscosity, when measured at each patient's own packed cell volume, was significantly higher in PSR positive males, this effect probably being attributable to the haemoglobin level, since multiple logistic regression analysis indicated no effect independent of haemoglobin and HbF levels. No differences were apparent between PSR and non-PSR groups in females. Plasma viscosity and erythrocyte filterability were not significantly different for either sex between patients with or without PSR.

Discussion

The only significant difference in rheological indices between PSR and non-PSR groups was an increase in

Table 1 *Some haematological features of the PSR and non-PSR groups in males*

Variable	*PSR +ve*		*PSR −ve*		*Significance of difference*	
	Mean	*SD*	*Mean*	*SD*	*t*	*p*
$\log_e$ (HbF+1)	1·11 (3·1)	0·62	1·60 (4·0)	0·61	−2·18	<0·05
Hb (g/dl)	8·9	0·9	7·9	0·9	2·89	<0·05
PCV (l/l)	0·268	0·032	0·237	0·027	2·80	<0·05
MCHC (g/dl)	33·2	1·9	33·4	2·6	−0·30	NS
MCV (fl)	88·5	7·7	90·3	13·3	−0·49	NS
MCH (pg)	29·4	2·7	30·8	4·9	−1·02	NS
$\log_e$ (reticulocytes+1)	2·44 (10·5)	0·29	2·41 (10·2)	0·39	0·01	NS
$\log_e$ (fibrinogen)	1·25 (3·3)	0·48	1·18 (3·3)	0·30	0·62	NS

t Test based on 15 matched pairs. NS=not significant. Figures in parentheses represent mean values re-expressed in original units.

Table 2 *Some haematological features of the PSR and non-PSR groups in females*

Variable	*PSR +ve*		*PSR −ve*		*Significance of difference*	
	Mean	*SD*	*Mean*	*SD*	*t*	*p*
$\log_e$ (HbF+1)	1·81 (5·1)	0·67	1·86 (5·4)	0·79	−0·15	NS
Hb (g/dl)	7·7	1·3	7·7	1·1	−0·04	NS
PCV (l/l)	0·228	0·037	0·241	0·033	−0·91	NS
MCHC (g/dl)	33·6	1·9	31·8	1·5	2·24	p<0·05
MCV (fl)	92·2	9·0	90·0	7·9	0·65	NS
MCH (pg)	29·9	3·3	30·2	2·9	−0·25	NS
$\log_e$ (reticulocytes+1)	2·21 (8·2)	0·44	2·35 (9·5)	0·42	−0·63	NS
$\log_e$ (fibrinogen)	1·24 (3·5)	0·26	1·23 (3·4)	0·22	0·07	NS

t Test based on 12 matched pairs. NS=not significant. Figures in parentheses represent mean values re-expressed in original units.

the male PSR group of whole blood viscosity measured at the patient's own packed cell volume. At the given shear rate (230 s^{-1}), viscosity measurements reflect erythrocyte deformability, since interactions between cells (for example, rouleaux) are prevented. The observation that significant differences emerged at the patient's packed cell volume but not when expressed at a standard packed cell volume (0·45) implies that the haemoglobin level in individual patients may be important.

Previous analyses of the haematological determinants of PSR[1] have indicated important sex differences, male patients with PSR having significantly higher haemoglobin and lower fetal haemoglobin (HbF) levels but no relationship being apparent in female patients. A similar pattern occurred in the present study, and in addition female PSR patients had a significantly raised MCHC.

The results of the present study were therefore consistent with previous findings in the haematological features and have added the observation of a significant difference in whole blood viscosity in males when measured at each patient's own packed cell volume. An apparent negative finding has been that erythrocyte deformability, as measured by the positive filtration technique, does not appear to differ between PSR and non-PSR groups. The presence of contaminating leucocytes in our test erythrocyte suspensions may have reduced the sensitivity of the method to alterations in erythrocyte deformability.[10] Thus high-shear viscosity measurements in this study were probably a truer reflection of erythrocyte deformability, and future filtration studies should employ a leucocyte depleted (to $<0{\cdot}025\times10^9$/l leucocytes) erythrocyte suspension.[11] Such studies are required to confirm whether haematocrit alone, as suggested in the present study, is the cause of hyperviscosity in males with PSR or whether a reduction in erythrocyte deformability is an additional factor.

There are additional problems in using these methods to determine the risk factors associated with the development of PSR. In most cases patients are being studied years after the development of PSR, and their current haematological and viscosity characteristics may not accurately reflect those at the time of development of PSR. Furthermore the group developing PSR may not be those with the greatest vaso-occlusive tendency, since, in these, occlusion of the abnormal arteriovenous communications that precede PSR may actually inhibit its development. Such a situation would differ from the well recognised

Table 3 *Comparison of viscosity and red cell filterability in PSR and non-PSR groups in males*

Variable	*PSR +ve*		*PSR −ve*		*Significance of difference*	
	Mean	*SD*	*Mean*	*SD*	*t*	*p*
Viscosity						
Plasma (mPas)	1·83	0·20	1·82	0·14	0·19	NS
Whole blood (own PCV)*	4·46	0·70	3·89	0·41	2·71	<0·05
Whole blood (PCV=0·45)	8·35	2·37	7·37	1·17	1·45	NS
Erythrocyte filterability						
Pi (mmHg)	15·7	2·6	17·4	5·9	−0·99	NS
Log$_e$ (slope 2+1)	0·99 (1·7)	0·37	1·16 (2·2)	0·34	−1·39	NS

t Test based on 15 pairs except * when calculated from 14 pairs with complete data. Figures in parentheses represent mean values re-expressed in original units.

Table 4 *Comparison of viscosity and red cell filterability in PSR and non-PSR groups in females*

Variable	*PSR +ve*		*PSR −ve*		*Significance of difference*	
	Mean	*SD*	*Mean*	*SD*	*t*	*p*
Viscosity						
Plasma (mPas)	1·83	0·16	1·79	0·11	1·02	NS
Whole blood (own PCV)	3·95	0·34	3·81	0·75	0·64	NS
Whole blood (PCV=0·45)	7·39	1·02	7·41	1·63	−0·04	NS
Erythrocyte filterability						
Pi (mmHg)	16·6	3·8	16·4	3·1	0·09	NS
Log$_e$ (slope 2+1)	1·05 (1·9)	0·29	0·84 (1·3)	0·26	1·64	NS

t Test based on 12 matched pairs. Figures in parentheses represent mean values re-expressed in original units.

autoinfarction of established PSR,[3] since PSR would not occur.

A reasonable working hypothesis for the development of PSR in sickle cell disease would recognise three groups of patients according to their vaso-occlusive tendency. Patients with the lowest vaso-occlusive tendency would not develop peripheral retinal vaso-occlusion and retinal infarction. Patients with intermediate indices would develop such occlusion and infarction, and abnormal arteriovenous communications would form at the junction of vascular and avascular retina from which the lesion of PSR would develop. Patients with the highest vaso-occlusive indices would develop retinal infarction but would also have occlusion of the abnormal arteriovenous communications, which would inhibit the development of PSR.

Such a hypothesis could explain the unexpected observations that the prevalence of PSR is highest in sickle cell-haemoglobin C (SC) disease and in sickle cell-β^+ thalassaemia, which are generally mild conditions associated with less evidence of vaso-occlusion. This hypothesis could also explain the lack of more dramatic differences between PSR and non-PSR groups in the present study, since, whereas the PSR group would represent those with moderate vaso-occlusive tendencies, the non-PSR control group may represent a mixture of those with high and low vaso-occlusive tedencies.

Testing this hypothesis requires an accurate method of assessing the vaso-occlusive tendency in an individual, and this must await a better understanding of the pathological mechanisms in sickle cell disease. Factors likely to affect this are the size, shape, density, number, and deformability of erythrocytes, the haemodynamic adaptations to anaemia, the nature of vessel walls, interactions between erythrocytes and endothelial cells, and possible contributions from other formed elements such as platelets and leucocytes. Studies of these individual components in groups of patients with and without PSR may contribute to this understanding. The present study has demonstrated the importance of haematocrit as a determinant of the raised whole blood viscosity in males with PSR.

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Vitelliform dystrophy and pattern dystrophy of the retinal pigment epithelium: concomitant presence in a family

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SUMMARY We describe three siblings presenting unusual pigmented dystrophic lesions of the fovea. The first sibling showed macroreticular dystrophy associated with butterfly shaped dystrophy in one eye and associated with vitelliform cyst in the other eye. The second showed the atrophic outcome of a vitelliform cyst with development of subretinal neovascular membrane in one eye and a radial pigmented macular dystrophy in the other eye. The third sibling had bilateral macular vitelliform lesions. This vitelliform patterned dystrophy of the retinal pigment epithelium may represent a new form that should be classified near Best's disease and the pattern dystrophies.

Pattern dystrophy is a term proposed some years ago[1,2] to define a group of dystrophies of the posterior pole of the eye characterised by the arrangement of clumps of retinal pigment in a figure-like fashion. The better known pattern dystrophies are reticular dystrophy,[3] butterfly-shaped dystrophy,[4] and macroreticular dystrophy.[5]

Best's disease[6] is a dystrophy of the retinal pigment epithelium whose appearance, at least at its onset, is that of a cyst of orange coloured material deeply located in the macula. Moreover vitelliform dystrophic lesions resembling those of Best's disease have recently been found associated with pattern dystrophies.[7,8]

Many features are common to pattern dystrophies, Best's disease, and vitelliform dystrophy: the presence of pigmented material in the retinal pigment epithelium, the usually autosomic dominant inheritance, and the reduced or flat electro-oculogram with a normal electroretinogram. These characteristics and the possibility of finding together patterned lesions with vitelliform lesions suggest that all these dystrophies may be correlated.

Here we report on a family in whom an association between various patterned and vitelliform pigmentary dystrophic lesions in different stages of evolution was found.

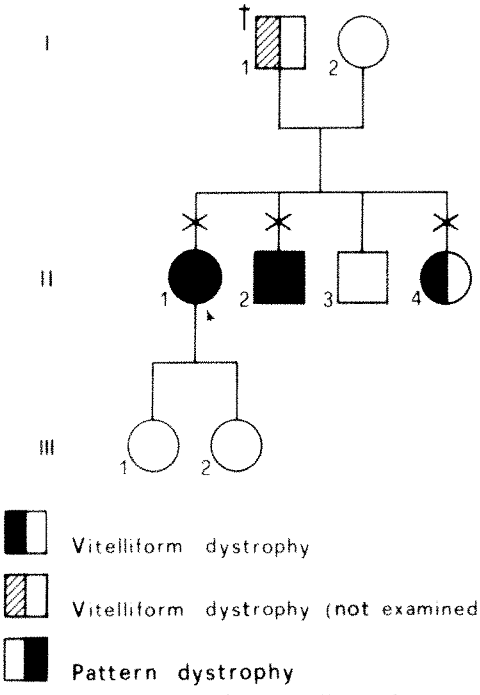

Fig. 1 *Pedigree of family with vitelliform dystrophy-pattern dystrophy of the retinal pigment epithelium. Autosomal dominant transmission is strongly suspected.*

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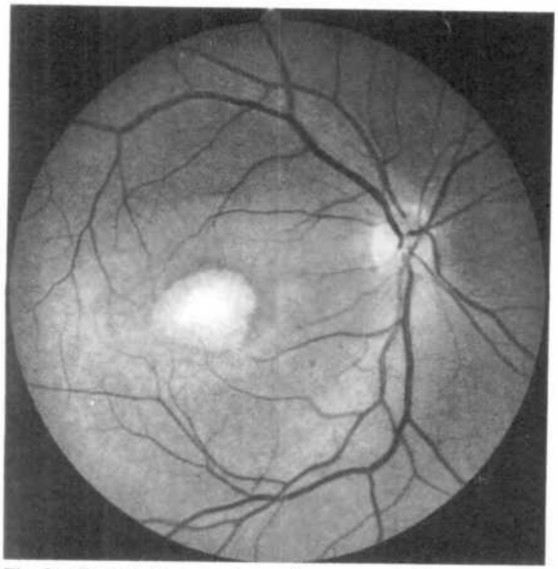

Fig. 2 *Case 1. An area of atrophy surrounded by some pigmented lesions is seen in the right macula.*

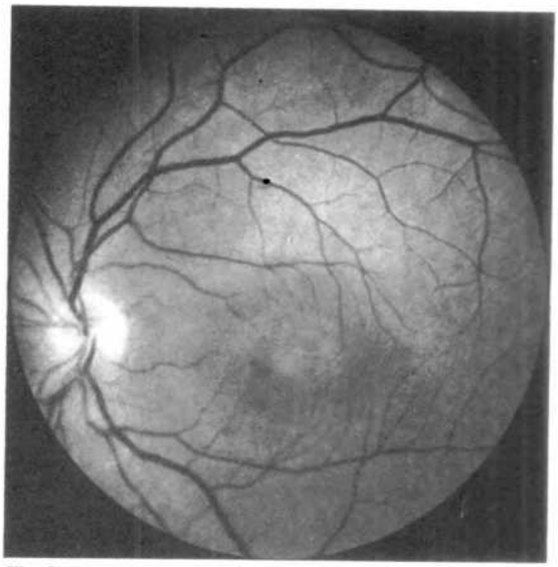

Fig. 3 *Case 1. Barely visible subretinal deposits occupy the left macular area.*

Case reports

CASE 1

This 26-year-old woman, the proband of the family shown in Fig. 1 (patient II, 1), had a history of abrupt visual loss in her right eye five months before we saw her. The corrected visual acuity was 20/100 in the right eye and 20/25 in the left eye. The anterior segment, intraocular pressure, and vitreous were normal.

Examination of the right fundus disclosed a round area of macular atrophy surrounded by small clumps of pigment (Fig. 2). In the macula of the left eye a subretinal greenish lesion was noted (Fig. 3).

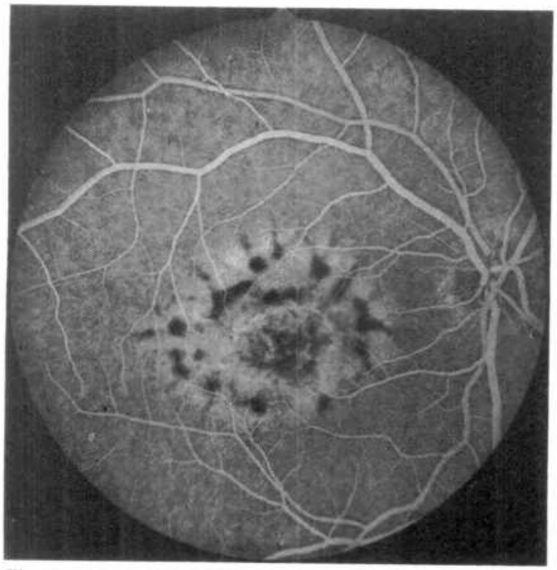

Fig. 4 *Case 1. Fluorescein angiography of the right eye, in the early venous phase, shows a net of subretinal macular capillaries. A crown of hypofluorescent lesions surrounds this zone.*

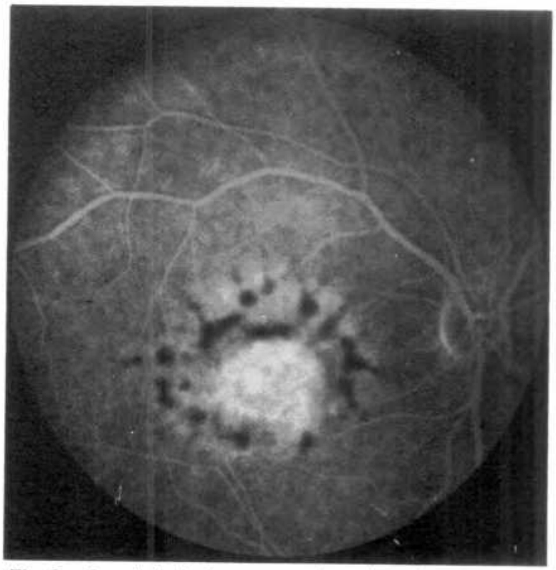

Fig. 5 *Case 1. In the late venous phase the subretinal choroidal neovascular membrane of the right eye shows profuse leakage.*

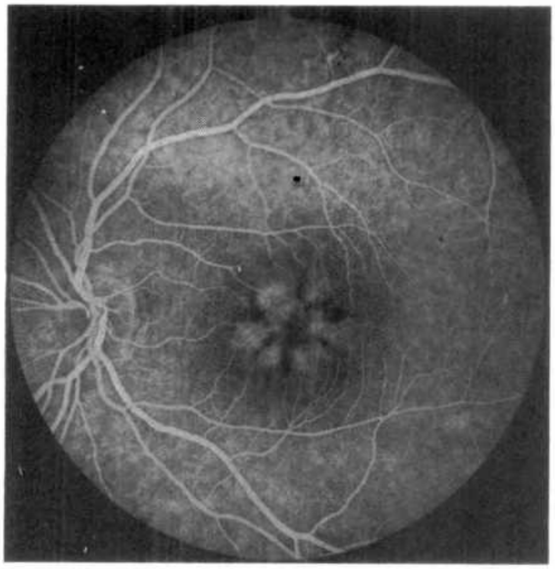

Fig. 6 *Case. 1. Fluorescein angiography of the left eye shows some hypofluorescent, radially orientated, macular lesions intermingled with hyperfluorescent areas.*

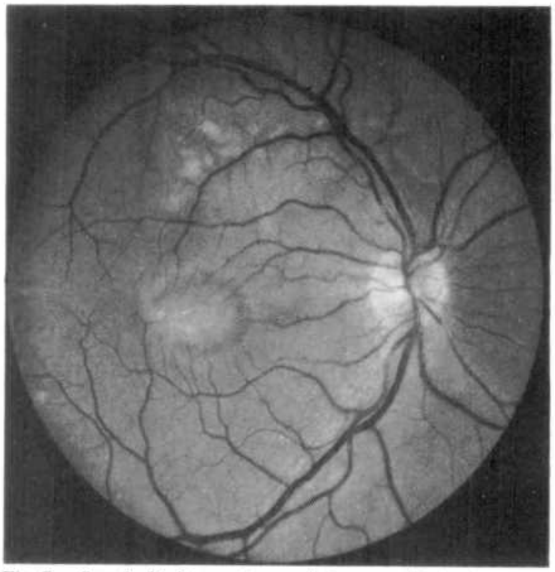

Fig. 7 *Case 2. Right eye. A round pigmented lesion is seen in the macular area. Along the superior temporal arcade there are punctate and linear deposits.*

Fluorescein angiography in the right eye revealed, under the atrophic area, a neovascular choroidal membrane leaking fluorescein in the venous phase (Figs. 4, 5). Many hypofluorescent dots scattered in a background of transmitted fluorescence surrounded the lesion. The left macular showed hypofluorescent radial streaks intermingled with hyperfluorescent zones (Fig. 6).

Kinetic visual fields (Goldmann perimeter) showed a reduced central sensitivity in the right eye. Colour sense, with the pseudoisochromatic tables of Ishihara, was normal. The scotopic and photopic electroretinograms recorded by the method used in our laboratory,[9] were normal. The electro-oculogram showed a flat curve in both eyes with absence of the light rise.

CASE 2

The 25-year-old brother of the proband (patient II, 2) complained of seing a shadow with his right eye. The corrected visual acuity was 20/25 in the right eye and 20/20 in the left eye. The anterior segment, intraocular pressure, and vitreous were normal.

Fundus examination showed a foveal yellow-green dot located under the retina in both eyes (Figs. 7, 8). Small yellow dots and streaks similar in appearance to the foveal lesion were distributed along the first tract of the superotemporal arcade.

Fluorescein angiography showed masking hypofluorescence of the lesions surrounded by hyperfluorescent areas. The macular lesion in the right eye (Fig. 9) was triangular and its major axis was one disc diameter wide, while in the left eye (Fig. 10) it was round and smaller. The pigmented streaks outlined a rough network above the macula.

Goldmann perimetry showed a small central scotoma with the target 0/1 in the right eye and normal features in the left eye. Colour sense was normal as

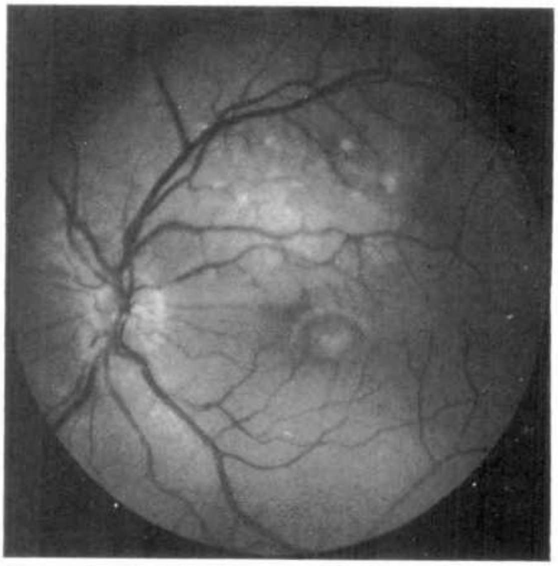

Fig. 8 *Case 2. In the left eye pigmented lesions similar in appearance to those of the contralateral eye are seen.*

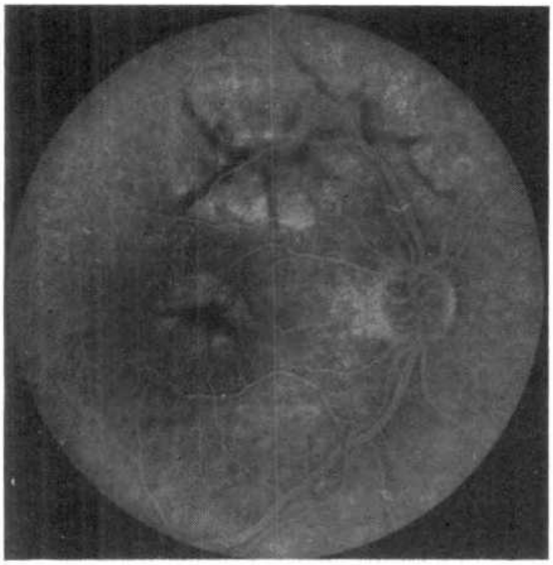

Fig. 9 *Case 2. In the right eye fluorescein angiography displays a triangular hypofluorescent macular lesion with a branching pattern in the upper posterior pole. The nearby fundus appears hyperfluorescent.*

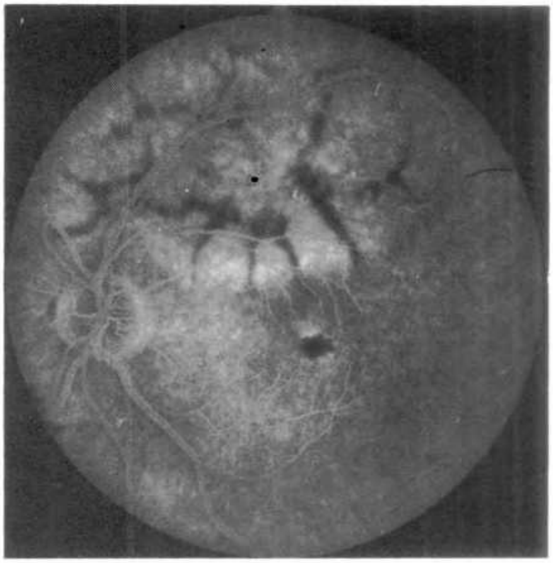

Fig. 10 *Case 2. Fluorescein angiography of the left posterior pole shows a round foveal hypofluorescent plaque surmounted by a reticular lesion.*

well as the scotopic and photopic electroretinograms. The electro-oculogram showed a very poor light rise with pathological Arden ratio (116 in both eyes).

CASE 3

The 18-year-old sister of the proband (patient II, 4) did not present with visual troubles. The visual acuity was 20/20 bilaterally. Nothing abnormal was found except in the fundus.

The fundus examination disclosed a round pigmented dot about half a disc diameter wide in the macula of both eyes (Figs. 11, 12).

The dots were hypofluorescent from the early phase of fluorescein angiography and were sur-

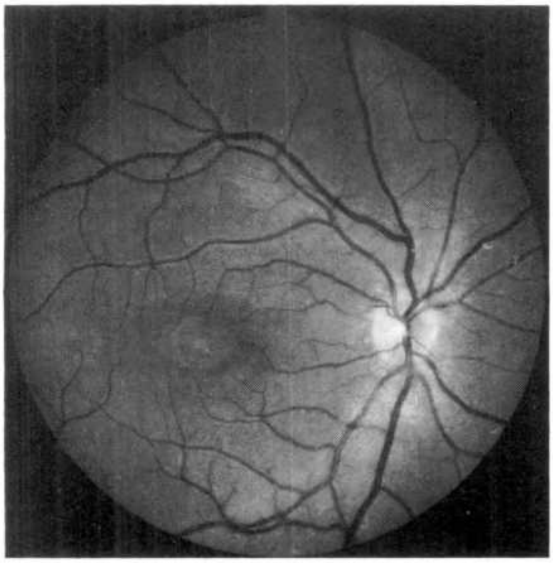

Fig. 11 *Case 3. The fundus of the right eye shows a pigmented subretinal central dot.*

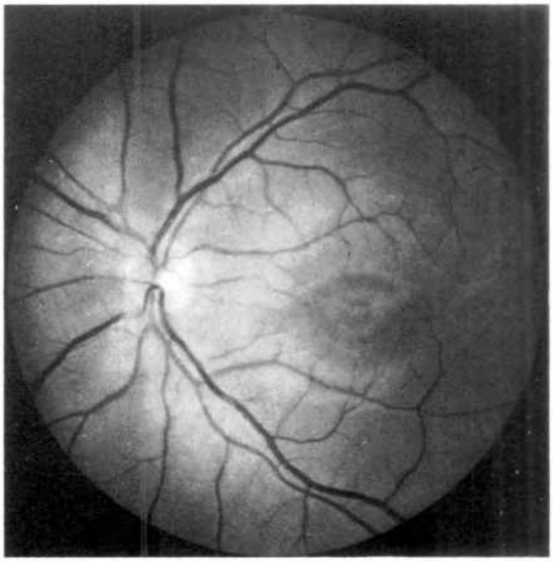

Fig. 12 *Case 3. The left macular displays the same features of the right eye.*

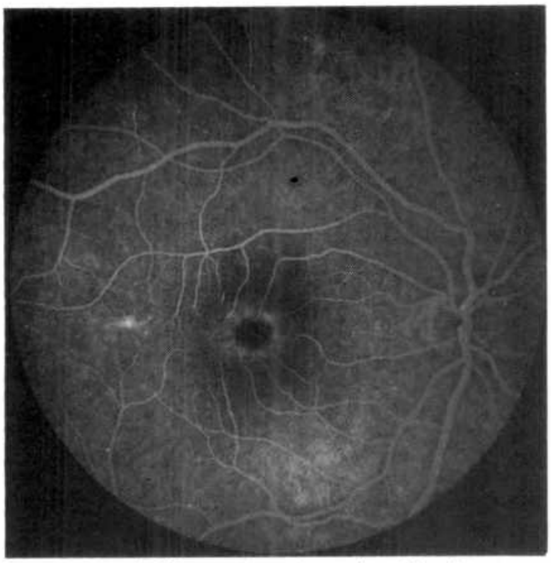

Fig. 13 *Case 3. Fluorescein angiography of the right eye. The macular lesion is hypofluorescent and it is surrounded by a hyperfluorescent pigment epithelial defect.*

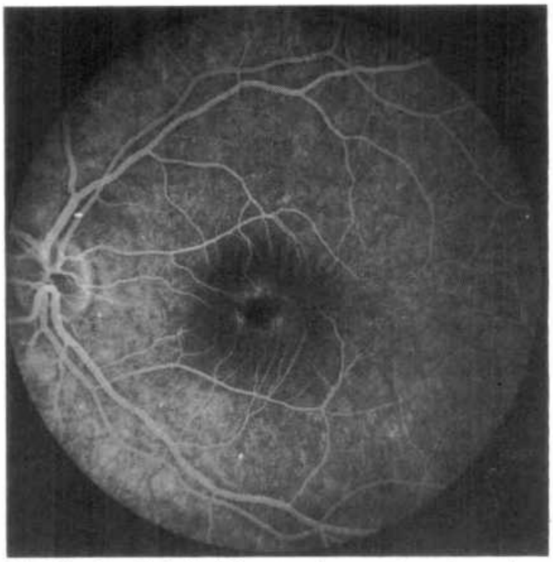

Fig. 14 *Case 3. In the left eye too fluorescein angiography shows a hypofluorescent central lesion highlighted by a ring of transmitted hyperfluorescence.*

rounded by a ring of transmitted fluorescence due to atrophy of the retinal pigment epithelium (Figs. 13, 14).

Visual fields, colour sense, and electroretinogram were normal. The electro-oculogram showed absence of light rise (Arden ratio=100) in both eyes.

It was impossible to examine the fourth sibling and the other members of the family. The father had been diagnosed before his death as having vitelliform dystrophy.

Discussion

The posterior poles of the retina of these three siblings show unusual pigmentary changes. The first sibling has in his right eye a central area of chorioretinal atrophy with subretinal neovascular membrane that probably represents the evolution of a vitelliform dystrophy. Round this lesion there are radial pigmentary streaks intermingled with areas of pigment epithelium rarefaction. In the left eye macular atrophy is absent, but there are pigmentary streaks in the fovea like those of the contralateral eye. In the second case the macular lesion of the right eye recalls the butterfly-shaped dystrophy of Deutman, while in the left eye the macular pigmentary material has a circular arrangement like vitelliform dystrophy. Above the optic disc there is a pigmentary lesion with a branched pattern like an eccentric macroreticular dystrophy. In this case too the pigment epithelium atrophy alternates with the hyperpigmentation. The third case shows a bilateral pigmentary change like vitelliform dystrophy surrounded by a ring of pigmentary rarefaction.

In all three cases the electro-oculogram is much impaired and the electroretinogram normal. Visual acuity is always good, with the exception of the eye with macular neovascularisation (case 1). The mode of inheritance of the lesions is probably autosomal dominant, but this can not be affirmed with certainty.

The macular lesions are obviously different expressions of a single pathological entity. It is probable that in all cases the pigmentary lesions are located, at least at the beginning, in the retinal pigment epithelium. The nature of the pigment is obscure: it could be composed of lipofuscin or some other material. However, no pattern dystrophy has been histologically examined so far. Recently the presence of lipofuscin in the retinal pigment epithelium in Best's disease was histologically proved.[10 11] Probably deposits of lipofuscin-like material also develop, in vitelliform dystrophy and in the pattern dystrophies, possibly owing to an enzymatic defect which reduces their degradation.[8 12]

The lesions seen in the family presented here have not been reported in other pattern dystrophies. Although some features of these lesions are common to previously described pattern dystrophies, they have enough distinctive features to allow us to regard this dystrophy as a new variety of the disease.

In particular, while the presence of various patterned pigmented lesions in members of the same family has often been described,[1,2,12-14] the association between patterned lesions and vitelliform lesions in a pedigree is much rarer. Some such associations have been reported, and these cases have features recalling the lesions here described, but no one of these single cases or families have all the characteristics of our pedigree. Gutman *et al.*[7] described a patient with vitelliform macular dystrophy in one eye and butterfly-shaped dystrophy in the other eye, and we[8] reported a case of vitelliform dystrophy associated with macroreticular dystrophy. A few other reports of this association have been described.[15-17] In all these cases the dystrophy was a vitelliform lesion surrounded by radial pigmented lines.

The resemblance between the vitelliform dystrophy that we observed and classic Best's disease is worth noting. Besides the similar morphological appearance the two forms have in common the flat electro-oculogram, the normal electroretinogram, and the autosomal dominant inheritance. So it is possible that vitelliform dystrophy represents a form of Best's disease associated with pattern dystrophy. However, at present it is preferable to restrict the term Best's disease to that entity which shows only round, dystrophic lesions of the pigment epithelium of the posterior pole, as described by Best,[6] and to define by the generic descriptive term 'vitelliform dystrophy' the lesions morphologically like the former but associated in the same patient or in other members of the family with patterned lesions.

A difference between vitelliform dystrophy and the pattern dystrophies lies in the alteration of the fundal lesions and the consequent visual outcome. The evolution of vitelliform dystrophy is probably similar to that of Best's disease, whose stages are well known.[18,19] In the early phases the lesion appears as a subretinal and hemispheric macular mass consistent with normal or slightly subnormal visual acuity. Subsequently the material of the cyst may precipitate in the inferior part of the cyst giving an appearance of pseudohypopion or can fragment, thus resembling scrambled eggs. In this stage the visual acuity is generally low. However, other vitelliform lesions never progress and others can even be reabsorbed. Their evolution may be more unfavourable, and the development of a subretinal neovascular membrane may ensue.[20,21]

Generally the event that causes the reduction of vision is fragmentation of the cyst. The reason for the rupture is not known. Probably an increase of the material in the cells of the retinal pigment epithelium causes their rupture.[19] This material spreads in the extracellular spaces and damage to the photoreceptors can follow.[10]

In the pattern dystrophies visual acuity is usually good in young patients but may become worse in the older people.[14,22,23] On the other hand in these dystrophies a dramatic and abrupt loss of vision as in Best's disease (and in vitelliform dystrophy) is never observed. This may be owing to the small dimensions of the macular lesions in the pattern dystrophies, which, affecting only a few cells of the retinal pigment epithelium, make an acute evolution with development of pseudohypopion or scrambled eggs lesion improbable. Although no follow-up of pattern dystrophies has been long enough to demonstrate their true evolution, we may presume that the macular lesion slowly progress, passing through a phase of pigmentary disorganisation and a later phase of atrophy.

Thus Best's disease and the various pattern dystrophies seem to have many clinical resemblances and some differences, especially in the morphology and the dimensions of the lesions. Some features of these two dystrophies are present in vitelliform pattern dystrophy, which may represent a new form correlated with the other dystrophies of the retinal pigment epithelium.

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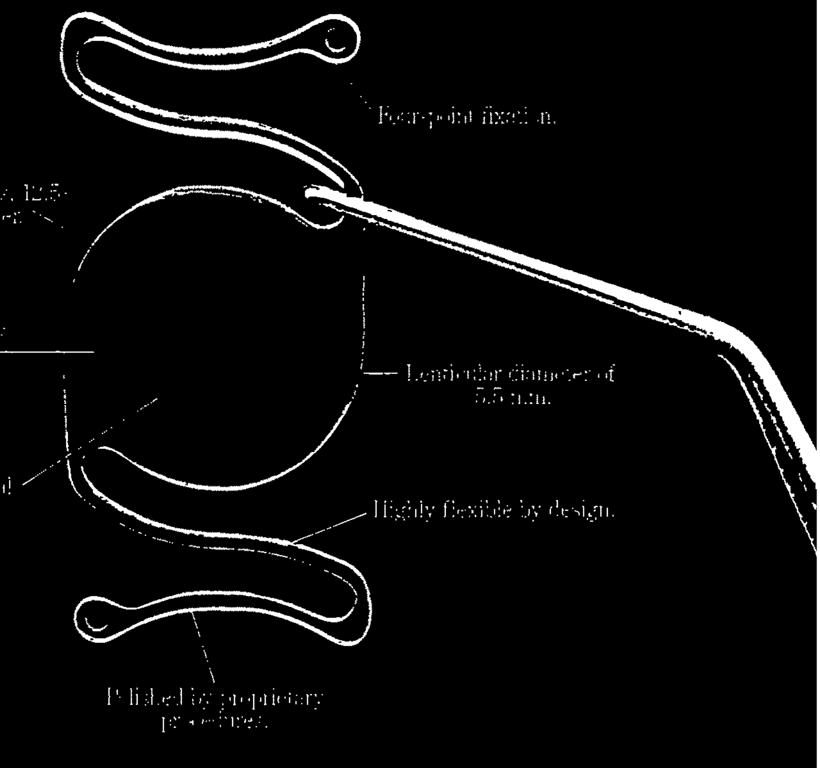
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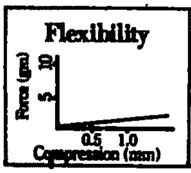

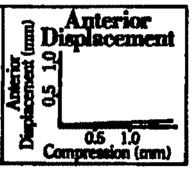

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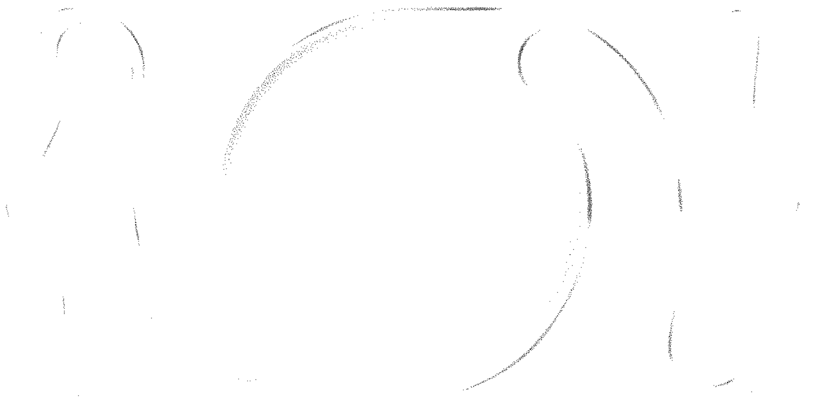

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Primary tuberculosis of the retina

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SUMMARY A case of pseudoglioma diagnosed on histopathology to be retinal tuberculosis is presented with a general review of the literature on ocular tuberculosis. The case is peculiar in that retinal tuberculosis occurred without concomitant involvement of the choroid.

In recent years very few cases of ocular tuberculosis have been reported.[1-8] They are limited to those illustrative cases where the diagnosis was unsuspected.[9,10] Tuberculous lesions in the eye have been mostly described in patients with concomitant evidence of a tuberculous focus elsewhere.[3-6,9] Primary tuberculous lesions in the eye have been rarely described in the orbit,[6,7] conjunctiva,[8,11] and retina.[12,13]

We describe here an interesting case of a child with histologically proved retinal tuberculosis but no evidence of any demonstrable tuberculous focus in the choroid.

Case report

A 3½-year-old male child was noted to have had for two months a yellowish pupillary reflex and loss of vision in the right eye (Fig. 1). There had been no redness of the affected eye. On examination the anterior segment was normal. There was no enlargement of the cornea or the eyeball. In the vitreous a yellowish mass originating from the retina was seen. The mass was moderately vascularised, and multiple haemorrhages were seen on its surface. No areas of calcification were seen on ophthalmoscopy. The mass occupied the whole retina. On trans-illumination the mass was opaque. The intraocular pressure under ether-nitrous oxide anaesthesia was 8·5 mmHg Schiøtz. The visual acuity in the left eye was 6/6 and clinically normal.

The child had no systemic abnormality. No significant lymphadenopathy was seen.

There was no similar history in the family. No history of consanguinity was available. The father and grandfather had tuberculosis before their death.

The right eye was enucleated.

The haemoglobin was 14·4 g/dl. A total leucocyte count gave $18\cdot2\times10^9$/l, lymphocytes 42%, neutrophils 56%, eosinophils 2%. The erythrocyte sedimentation rate was 16 mm in the first hour.

X-ray of chest showed a healed focus of tuberculosis at the apex of both lungs. *X*-ray of the orbits was normal, with no calcification. *X*-ray of the optic foramina and superior orbital fissure was normal. Serological test for syphilis (VDRL) was negative. Tuberculin skin test was positive.

HISTOPATHOLOGY

On gross examination a firm mass was seen involving the retina, which was detached. The surface was vascularised and a few haemorrhages were seen. The optic nerve stump was of normal thickness and consistency.

Microscopic examination showed inflammatory granulomas in the retina with pale staining centres of caseous necrosis surrounded by epithelioid cells and lymphocytes (Fig. 2). Occasional giant cells were also seen. Acid-fast bacilli could not be demonstrated. Few blood vessels were seen. The iris, ciliary body,

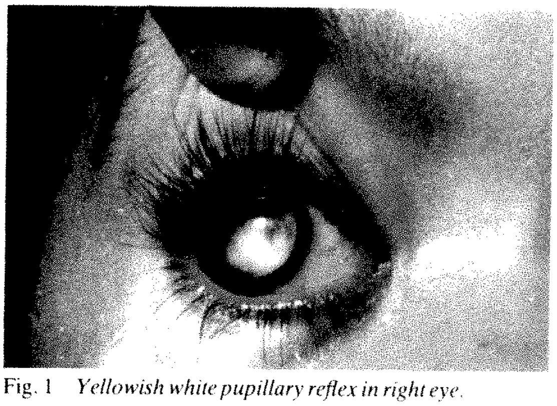

Fig. 1 *Yellowish white pupillary reflex in right eye.*

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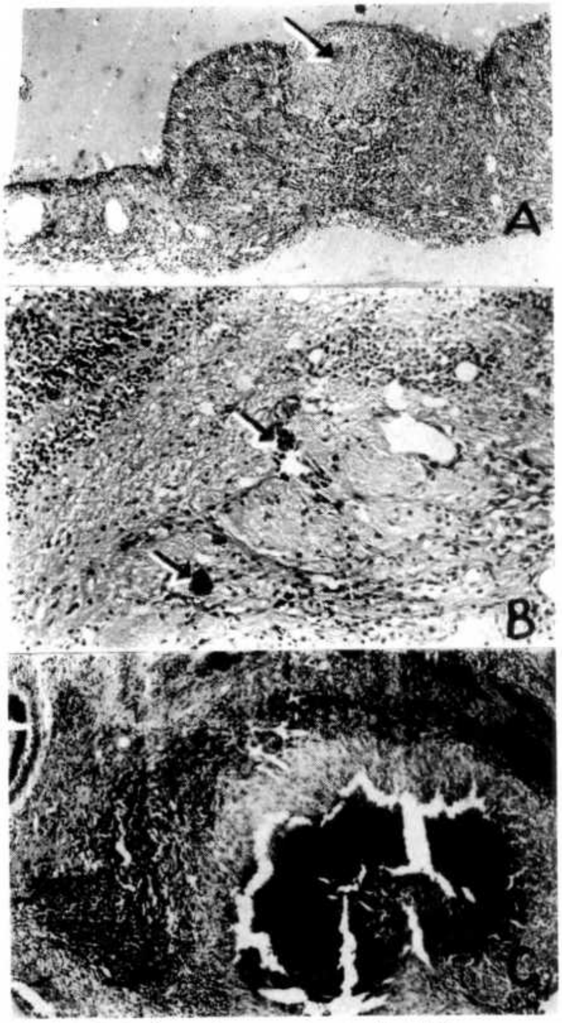

Fig. 2A: *Retinal granulomatous (arrowed). (×50).*
B: *Granuloma consisting of central necrosis, epithelioid cells, lymphocytes, and giant cells (arrowed). (×127).*
C: *Granuloma consisting of caseous necrosis, epithelioid cells, lymphocytes. (×127). (All haemotoxylin and eosin).*

and choroid did not show any granuloma. No evidence of inflammation was seen in the sclera and optic nerve stump.

Discussion

Among the causes of leucocoria intraocular tuberculous inflammation is considered to be uncommon.[14] The criteria for diagnosing ocular tuberculosis include the presence of tubercles composed of epithelioid cells and giant cells, caseation necrosis, rarely the presence of acid-fast bacilli, and evidence of systemic tuberculosis.[15 16] Failure to demonstrate acid-fast bacilli is not considered to be an evidence against a tuberculous aetiology by many authors.[14 17]

In our patient pseudoglioma was considered in view of low intraocular tension and absence of calcification radiologically in the affected eye. On histopathology typical discrete tubercles with central caseous necrosis surrounded by epithelioid cells, lymphocytes, and occasional giant cells were seen in the retina. The choroid, iris, ciliary body, and the region of the optic nerve head showed no such inflammation. Though no acid-fast bacilli could be demonstrated, we consider that the histopathological findings are quite characteristic of tuberculosis.

Radiological evidence of a healed pulmonary tuberculous lesion, a positive tuberculin test, and a family history of tuberculosis are other corroborative features in our case. Granulomatous retinal inflammation is also described in syphilis in which a positive serology and systemic features are diagnostic. In sarcoidosis, in which involvement is usually bilateral, the lesions are chorioretinal, anterior uveitis is more common, and radiological evidence of perihilar adenopathy and skeletal changes is diagnostic. Parasitic infestations causing granulomas are described in toxoplasmosis, toxocariasis, and certain other nematode infestations. Granulomatous inflammation in parasitic infestations always show eosinophils and plasma cells in addition to lymphocytes on histopathological examination. Also direct evidence of the presence of parasites in the inflamed tissue can be obtained on histopathological examination.

Tuberculosis of the retina is uncommon in contrast to that of the choroid[18] and occurs more often in acute general miliary tuberculosis or by extension from other parts of the eye. Primary retinal tuberculosis has been rarely described before.[12 13] Ocular tuberculosis has been described with a concomitant tuberculous focus in lungs,[6 9 10] long bones,[3] and spine.[4] The diagnosis of extrapulmonary tuberculosis, especially ocular tuberculosis, is riddled with difficulties due to lack of inadequate investigating facilities[4] and the relative rarity of acid-fast bacilli in the lesions.[17] Because of the difficulties in clinching a specific diagnosis most eyes with pseudoglioma due to intraocular tuberculosis have been enucleated under a mistaken diagnosis of retinoblastoma.[9 10 13] Ocular lesions in tuberculosis are mostly due to haematogenous spread from a systemic focus, including lymph nodes. We believe that in our patient retinal granulomatous inflammation occurred secondarily to a systemic tuberculous focus, possibly in lymph nodes. We suggest that retinal tuberculosis should be suspected in all eyes with pseudoglioma, particularly in the developing countries, where tuberculosis is still rampant.

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Ophthalmia nodosa and the oculoglandular syndrome of Parinaud*

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SUMMARY We present a case of ophthalmia nodosa and Parinaud's oculoglandular syndrome in a patient scratched by a cat six and a half months previously and who gave a positive result to an antigen test for cat scratch disease. In conjunctival swabs were also found urticarial hairs, tracheal fragments, processionary caterpillar oenocytes, and a grain of pollen. The pathogenic part played by each of these foreign bodies is discussed, as well as the possibility of the oculoglandular syndrome being due to the reactivation of a latent virus, the organism of cat scratch disease. So far as we know, this work provides the first description of the association of ophthalmia nodosa with the oculoglandular syndrome of Parinaud.

The hairs of certain insects or plants can penetrate the conjunctiva and the cornea to produce an inflammation named ophthalmia nodosa. The severe ocular reaction is the combined effect of two separate components, one mechanical and the other toxic.[1] The term 'ophthalmia nodosa' derives from the nodular conjunctival reaction.[2] Depending on the regions, the cause of the ophthalmia nodosa is mainly the needles of plants, such as the common burdock,[1 3 4] or urticarial hairs of some caterpillars.[5-7] According to Watson and Sevel[8] only six varieties of caterpillars are known to cause ophthalmia nodosa. *Macrothylacia rubi* and *Arctia caja* are found only in the British Isles, while *Thaumetopoea pityocampa* Schiff (pine processionary), *Thaumetopoea jordana*, *Isia isabella*, and *Dendrolimus pini* may be found in other countries. Two other species may be added to these, namely *Thaumetopoea pinivora*, another pine processionary, and *Thaumetopoea processionnea* L., an oak processionary.[9] Furthermore, the oak processionary is supposed to have a greater urticarial impact than the pine caterpillar.[10]

The oculoglandular syndrome[11] is defined as a unilateral granulo-conjunctivitis associated with one or several pretragal and/or submaxillary adenopathies. Although in several cases the patients either had been scratched or had simply come into contact with cats, many other causes of the disease have been reported (Table 1).

The explanation for the unusual association in the same patient of an ophthalmia nodosa and of an oculoglandular syndrome is suggested from histopathological examination of the lesions.

Table 1 *Causes of the oculoglandular syndrome*

Diseases	*Responsible agents*
Frequent	
Cat scratch disease	Unknown
Tularaemia	*Francisella tularensis*
Sporotrichosis	*Sporothrix schenkii*
Occasional	
Tuberculosis	*Mycobacterium*
Syphilis	*Treponema pallidum*
Coccidioidomycosis	*Coccidioides immitis*
Rare	
Pasteurellosis	*Pasteurella septica Yersinia pseudotuberculosis, y. enterocolitica*
Equinia	*Actinobacillus mallei*
Chancroid	*Haemophilus ducreyi*
Venereal lymphogeanuloma	*Chlamydia trachomatis* L, L2, L3
Listeriosis	*Listeria monocytogenes*
Actinomycosis	*Actinomyces israelii*
Blastomycosis	*Blastomyces dermatidis*
Mumps	*Paramyxovirus*
Infectious mononucleosis	Epstein-Barr herpes virus
Spotted fever	*Rickettsia conorii*

Modified according to Chin and Hyndiuk.[24]

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*A part of this work was presented as a poster at the SSO meeting, Lausanne, 1984.

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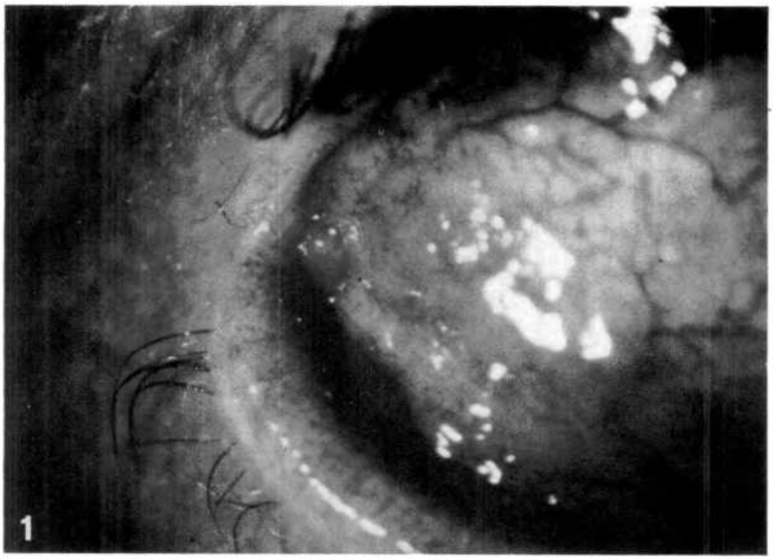
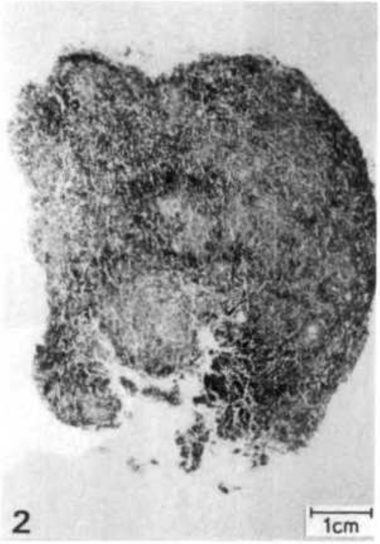




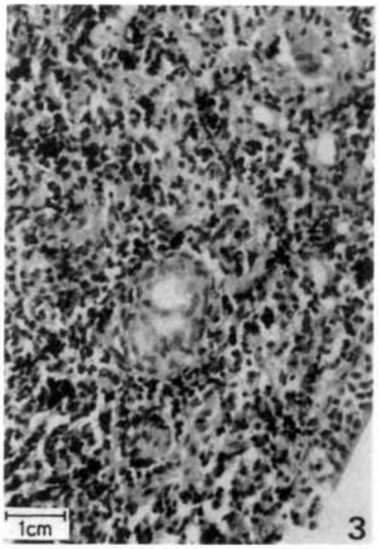


Fig. 1 *Characteristic aspect of the nodular lesions in ophthalmia nodosa.*

Fig. 2 *Macroscopic, nodular conjunctival lesion. (H–E, scale=200 μm).*

Fig. 3 *Typical nodule in ophthalmia nodosa, centred by a caterpillar hair. Same slide as in Fig. 2. (H–E, scale=50 μm).*

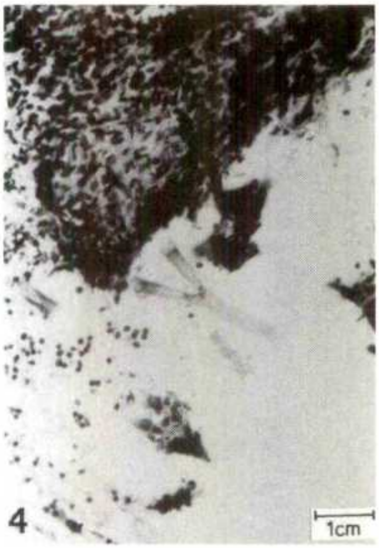
Case report

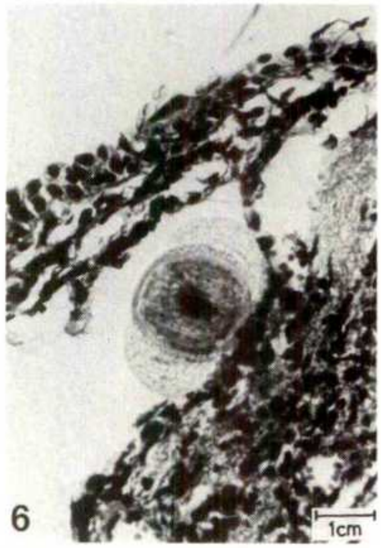
CASE HISTORY AND STATUS OF THE EYE

A 56-year-old man, without a history of ocular disease, came to our outpatient department on 28 February 1983 suffering from unilateral conjunctivitis of the right eye since 21 February 1983. On examination, we observed conjunctival injection and marked inferior temporal chemosis but an unscathed cornea. The condition deteriorated in spite of an initial treatment with neomycin and bacitracin, followed by neomycin, polymyxin B, and dexamethasone. Taking a second case history revealed that six and a half months earlier the patient had been scratched on the forehead and right eyelid by a cat. Around mid February 1983, a few days before the beginning of the conjunctivitis of the right eye, the patient had pulled down a caterpillar nest from a pine in his garden without taking any precautions.

On 18 March 1983, the right pretragal gland, palpable since the beginning of the disease, had become very enlarged and painful, measuring 5 by 7 cm; the conjunctival lesion of the right eye remained unchanged. Various investigations (general, ear, nose, and throat, blood tests) all gave normal results.

The patient's condition did not improve in spite of





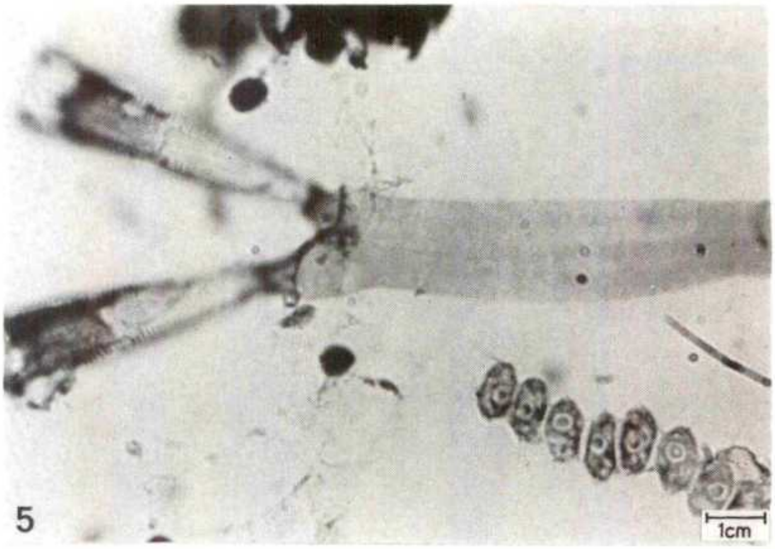


Fig. 4 *Tracheal fragments of the processionary caterpillar found in the conjunctival lesion. (H–E, scale=55 μm).*

Fig. 5 *Tracheal fragments and eight oenocytes of the processionary caterpillar. Same slide as in Fig. 4. (H–E, scale=20 μm).*

Fig. 6 *Grain of pollen found in the conjunctival lesion. (H–E, scale=30 μm).*

local and general antibiotic therapy (Spiramycin 2 g daily). Consequently on 29 March 1983 we performed an incision and drainage of the swollen gland. Examination (aerobic and anaerobic cultures) proved negative, and histological examination led us to the conclusion of reticulo-abscess lymphadenitis compatible with cat scratch disease. On 1 June 1983 we excised the conjunctival lesion, which had not regressed in spite of local treatment (Fig. 1). Histopathological examination showed the presence of granulomas containing foreign bodies, caterpillar hairs, tracheal fragments, caterpillar oenocytes, and a grain of pollen. On 13 June 1983 a thorough examination of the eye showed no other ocular lesion. On 20 June 1983 an antigen test for cat scratch disease proved to be positive after 48 hours.

At follow-up on 25 June 1983 the patient was regarded as cured.

PATHOLOGY OF THE CONJUNCTIVAL LESION

Macroscopically. Characteristic nodular lesion measuring 5 mm in length, 2 mm in width, and 1·5 mm in height were observed. They were whitish yellow in colour, firm in consistency, and not adherent below (Fig. 2).

Microscopically. On light microscopy the conjunctival stroma was highly infiltrated by lymphocytes in which were found various badly delimited nodules

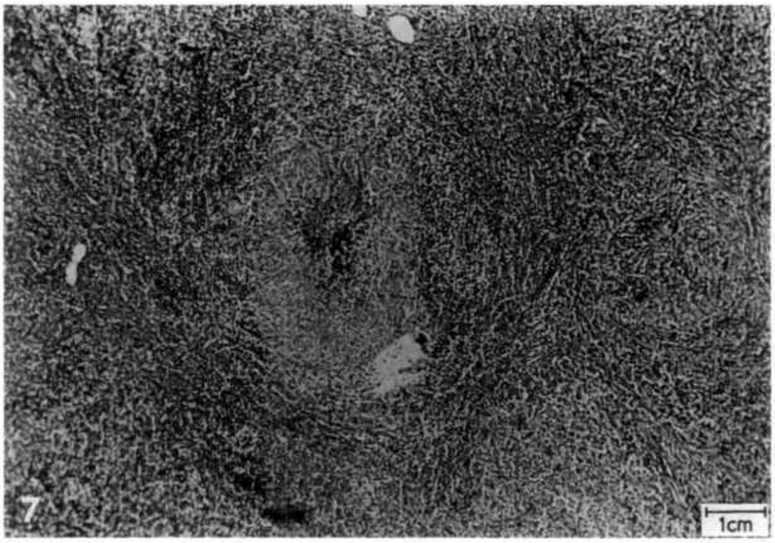


Fig. 7 *Granuloma photographed within the pretragal adenopathy. (H–E, scale=127 µm).*

made up of epithelioid cells and sometimes of giant multinucleated cells of the foreign body type. Serial slides showed various structures—caterpillar hairs (Fig. 3), tracheal fragments, oenocytes (Figs. 4 and 5), and a grain of pollen (Fig. 6). Although the circumstances of the onset of this condition, the macroscopic appearance of the lesion, and its histological appearances were pathognomonic according to Malan,[12] we wanted to ascertain whether the foreign bodies found on the slides did in fact come from processionary caterpillars.

PATHOLOGY OF THE PRETRAGAL ADENOPATHY

Histological examination showed a ganglionic stroma with micro-abscesses surrounded by histiocytes (Fig. 7). The histological image was compatible with cat scratch disease.

Morphology of the processionary caterpillar

The caterpillars studied, *Thaumetopoea pityocampa* Schiff, were captured at the larval stage on a black pine *(Pinus nigra)* in mid November 1983. Scanning electron and light microscopic examination allowed us to compare and recognise the various foreign bodies found in the conjunctival swab.

THE INSECT EYE AND URTICARIAL HAIRS

Urticarial hairs are implanted on the facets of the insect 'mirror',* including two small posterior and two large anterior facets (Figs. 8 and 9). The hairs found elsewhere on the caterpillar body were not urticarial and did not become detached spontaneously. Experimental studies on the rabbit eye with hairs other than the urticarial ones of the insect eye did not provoke ophthalmia nodosa.[13]

TRACHEAL FRAGMENTS

The tracheal apparatus, highly developed in the caterpillar, is subdivided into a multitude of small tracheas, the smallest of which is intercellular.[14]

Discussion

In Switzerland ophthalmia nodosa is mainly caused by urticarial hairs of the pine processionary caterpillar. Their urticarial hairs, constituent elements of the 'mirror', measure from 0·08 to 0·16 mm depending on the age of the caterpillars.[15] Contrary to what is generally thought, the hairs surrounding the 'mirror' do not play any part in the releasing of the hairs. When a 'mirror' opens, the hairs are carried away by the wind and break up at the slightest contact, thus releasing an unknown urticarial substance.[16] When the urticarial hairs penetrate the human eye by an as yet unknown means,[17,18] they cause various complications, such as hypopyon ulceration, iritis, iridocyclitis, cataract, and even retinal detachment.[19-21] The eyelid and conjunctival lymphatic drainage is carried out by means of the pretragal glands for the external part and by the submaxillary glands for the internal part.[22] In this case the lesion situated in the conjunctival sac near the external angle is therefore related to the pretragal adenopathy, described as Parinaud's oculoglandular syndrome. However, so far as we know, ophthalmia nodosa has never been

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*'Mirror' or group of papillae (Beille, 1896), cited by Pesce H, Delgado A. Poisoning from adult moths and caterpillars. In: Bücherl W, Buckley EE, eds. *Venomous animals and the venoms*. New York: Academic Press, 1971; **3:** 142.

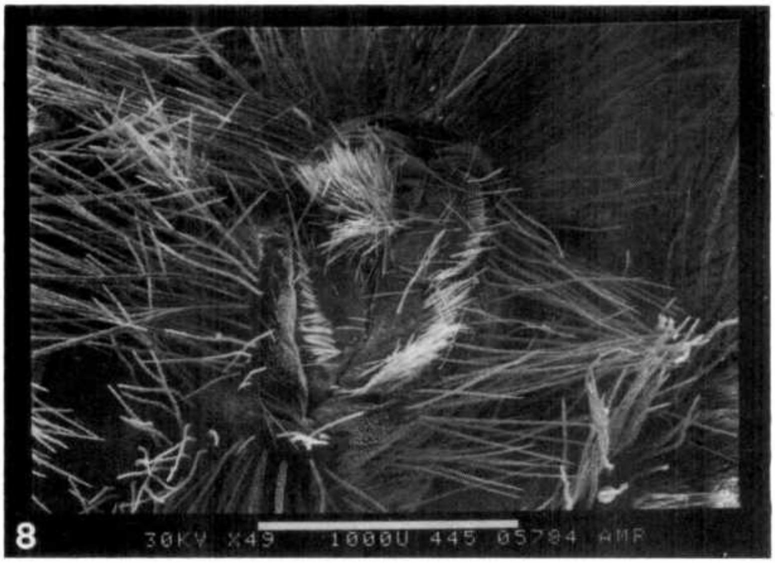

Fig. 8 *Open mirror of the pine processionary caterpillar* Thaumetopoea pityocampa *Schiff (larval stage L4). Scanning electron microscopy. (Electron Microscopy Center of the Medical Faculty, Lausanne University. Scale=1 mm).*

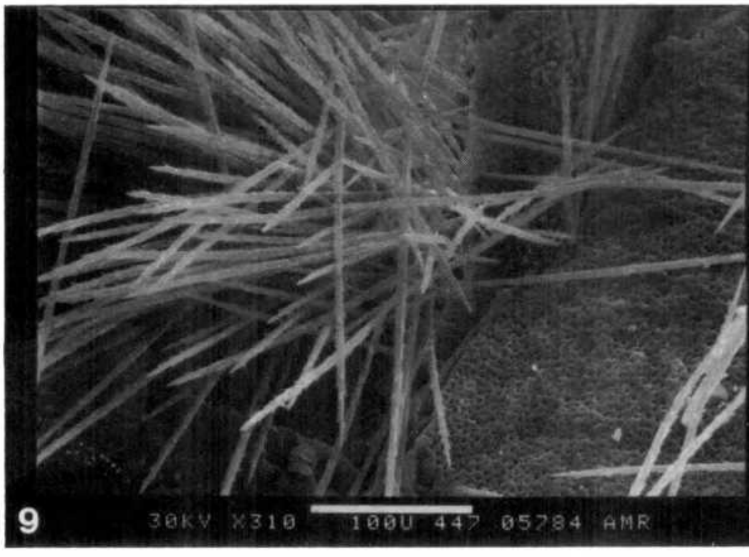

Fig. 9 *Urticarial hairs. Enlargement of a bunch of hairs on the left upper facet of the mirror shown in Fig. 8. (Scale=100 µm).*

described in association with an oculoglandular syndrome,[3,8,23,24] nor has the oculoglandular syndrome, with cat scratch disease as its most frequent cause, ever been described as appearing later than the sixth week after the scratching.[25-27] Thus we realise that pretragal adenopathy is related not only to caterpillar hairs but also to some other pathogenic element, such as tracheal fragments, oenocytes, pollen, the cat scratch disease agent, or another.

TRACHEAL FRAGMENTS AND OENOCYTES

It was possible to identify tracheal fragments and oenocytes found in conjunctival tissue through a review of the entomological literature,[14,28-31] and from a comparison between the conjunctival and caterpillar slides. Oenocytes are cells of ectodermal origin, usually found in chain formation on the caterpillar walls[31] in the vicinity of the trachea.[14] The oenocytes produce lipoprotein, probably carried by oenocytoids. These lipoproteins are necessary for the formation of the caterpillar's cuticle.[32] Are the oenocytes and their lipoproteins the responsible antigens or co-antigens in causing the adenopathy? If this were so, the association would probably be known, because when destroying a caterpillar nest one is exposed to hairs as wells as to fragments.

POLLEN

Even though the patient had several types of allergy—for example, to penicillin and streptomycin—we think it most improbable that a black-pine pollen grain could be the cause of the oculoglandular syndrome. Clinical and laboratory tests possibly failed to reveal some other pathogenic agent, contracted by the patient at the same time or transmitted by the caterpillar fragments.

OTHER PATHOGENIC ELEMENTS

It is seldom that a second pathogenic agent is associated with the hairs of the processionary caterpillar. The only reported case was one described by Rhoner and Huber,[33] who, after having enucleated an eye for aspergillosis, found a caterpillar hair in the vitreous body. In the case we present here mycological tests proved to be negative.

CAT SCRATCH DISEASE

The cause of cat scratch disease is unknown, but atypical bacteria,[34] chlamydia, and a herpes-like virus[35] are possible. The scratches on the homolateral eyelid that the patient received six and a half months before the ophthalmia nodosa, the histological appearance of the adenopathy, and the presence of a positive antigen test to cat scratch disease all suggest the presence of this disease, whose causal agent, as in herpes infection, remains latent. So far as we know this report provides the first description of the association of ophthalmic nodosa and the oculoglandular syndrome of Parinaud.

We are very grateful to Ms Anne Fischer-Cassiot, who allowed us to consult her most interesting work on the processionary caterpillar, and to Mr Max Hachler for his advice, both working at the Federal Centre of Agronomic Research at Changins, and to Mr Alexander Cotty, of the Zoological Museum of Lausanne. We also thank Dr Robert Brun, lecturer at the Geneva Medical Faculty, for kindly giving us the cat scratch disease antigen, Ms Madeleine Martin for typing the article. Ms Françoise Sallaz for bibliographic research, Ms Letitia van der Linden for the English translation, and Dr Phillip Hendrickson, University Eye Hospital, Basle, for proof reading the text.

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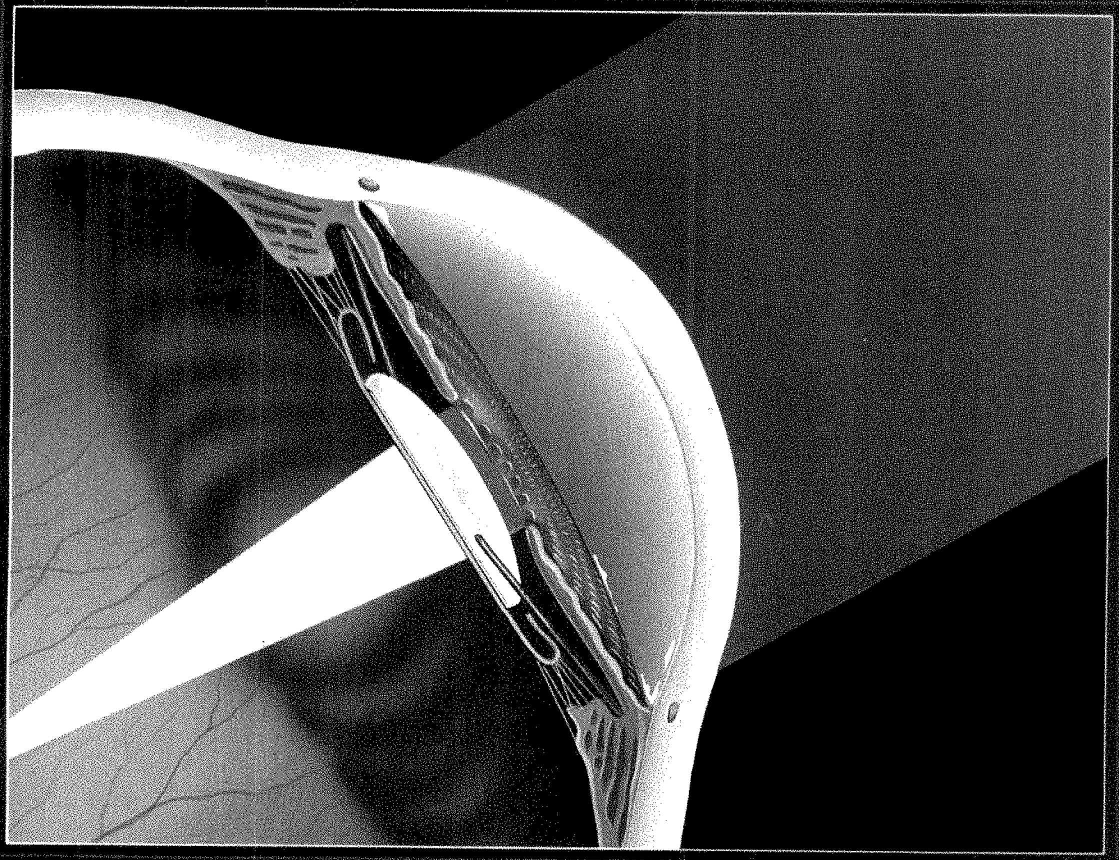

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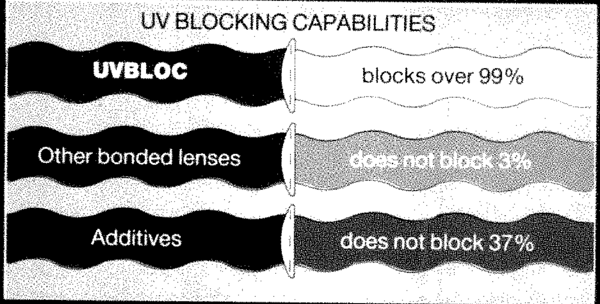

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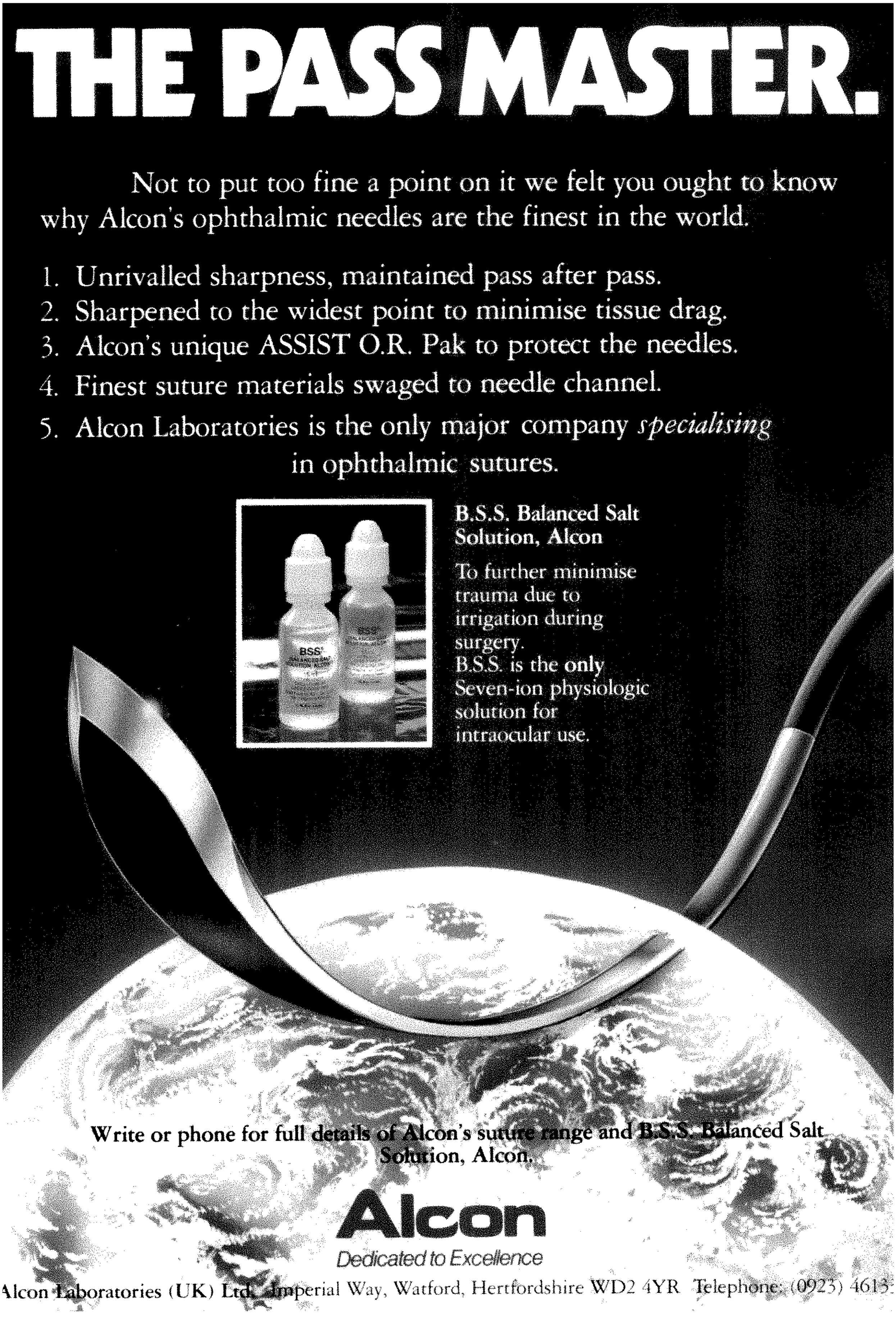
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Primary intraorbital extraocular primitive neuroectodermal (neuroepithelial) tumour

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SUMMARY A case is reported of primary primitive neuroectodermal (neuroepithelial) tumour occurring in the right orbit of a 52-year-old man. The intraorbital extraocular location is unique for this kind of neoplasm. The malignant tumour was differentiated into primitive neuroepithelial, ependymal, and oligodendroglial cells. The neuroglia was identified by localisation of cytoplasmic glial fibrillary acidic protein. It is suggested that this primary intraorbital, extraocular, primitive neuroectodermal tumour with neuroglial differentiation is akin to the primitive neuroectodermal tumours of the neuraxis, including the cerebellar medulloblastomas, and to some peripheral nerve tumours known as malignant neuroepitheliomas, malignant ependymomas, and neuroblastomas. The ectomesenchymal remnant of the neural crest or ectopic neuroepithelium or both may have been the origin of the present tumour. Differentiation of the neuroectodermal component of the neural crest or heterotopic neuroepithelium or both would create a primitive neuroectodermal tumour with diverse neuroglial elements.

Primitive neuroectodermal tumours of the neuraxis[1-3] and peripheral nerves[4,5] have been described. However, we are unable to trace a report of the same type of tumour arising primarily within the orbit but outside the eyeball. In this communication we describe a primary intraorbital, extraocular, primitive neuroectodermal tumour occurring in an adult man.

Case report

A 52-year-old man was admitted to hospital because of progressive right exophthalmos for one month. He denied ocular pain, blurred vision, diplopia, and other systemic symptoms.

Physical examination revealed a body temperature of 37°C, pulse rate 85 beats/min, respiratory rate 20/min, and blood pressure 150/90 mmHg. The right eye showed mild oedema of the eyelids and proptosis. Each pupil, 3 mm in diameter, was reactive to light. Ocular movements were bilaterally full in all directions. The fundi showed constriction of the arterioles. No papilloedema or intraocular tumour was observed. Cranial nerves, visual field, and visual acuity were normal, as were other systems of the body and various laboratory tests. No abnormal masses were detected in any part of his body.

Computerised tomographic (CT) scans of the orbits and brain disclosed a right enlarging intraorbital tumour located laterally. The right eyeball and optic nerve were displaced medially (Figs. 1, 2). No intracranial lesions were seen.

The patient underwent Krönlein's operation three weeks after admission to hospital. The outer wall of the right orbit was resected. The laterally situated intraorbital extraocular tumour was found to be unencapsulated and attached to the lateral rectus muscle. There was no bone invasion. The lesion was removed as much as possible. No connection between the tumour and any nerve was observed. It appeared clinically to be a neoplasm of the lacrimal gland.

PATHOLOGICAL EXAMINATION

The formalin-fixed tissue fragment was white, firm, and 3·5 × 4·0 × 4·0 cm. It was embedded in paraffin

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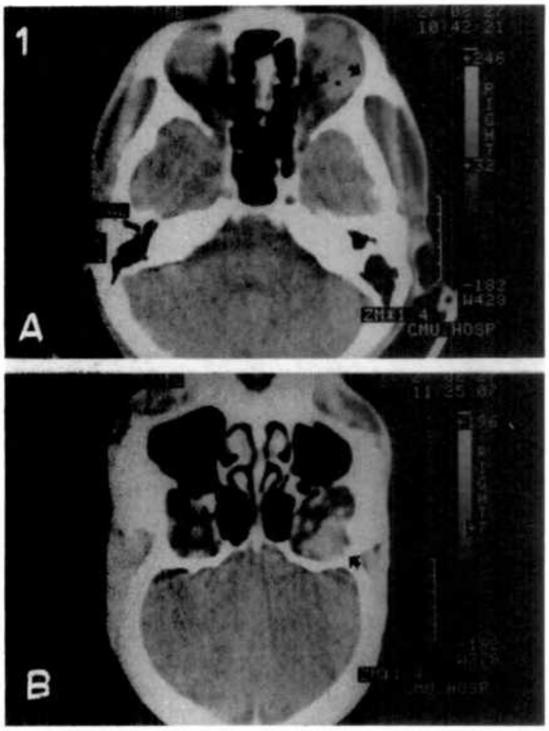

Fig. 1 A, B *Axial and coronal CT scans of the orbits show an infiltrative soft tissue mass in the superolateral part of the right orbit (left arrows) with pressure effect on the lateral wall (right arrows).*

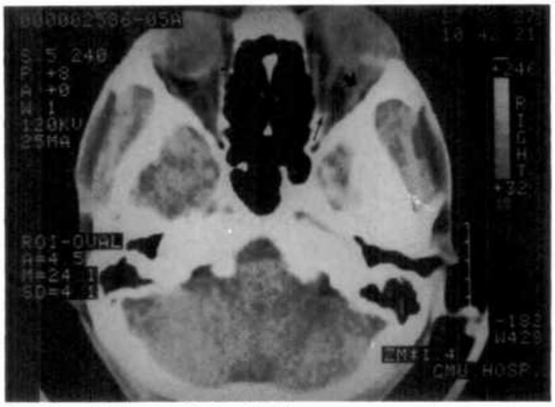

Fig. 2 *Axial cut at the level of the optic nerves demonstrates a mass invading into the right lateral rectus muscle (thick arrow). Note also medial displacement of the right optic nerve (thin arrow) and mild proptosis of the right eyeball.*

and sections were stained with haematoxylin and eosin (H–E). The following special stains were done: Mallory's phosphotungstic acid haematoxylin (PTAH) for neuroglial fibres, Gomori's stain for reticulin fibres, and Nissl's stain for neuronal tigroid substance.

The peroxidase-antiperoxidase technique was applied for immunohistochemical localisation of glial fibrillary acidic protein (GFAP) in formalin-fixed and paraffin-embedded tissue sections. A fragment of the normal brain was similarly processed as a control.

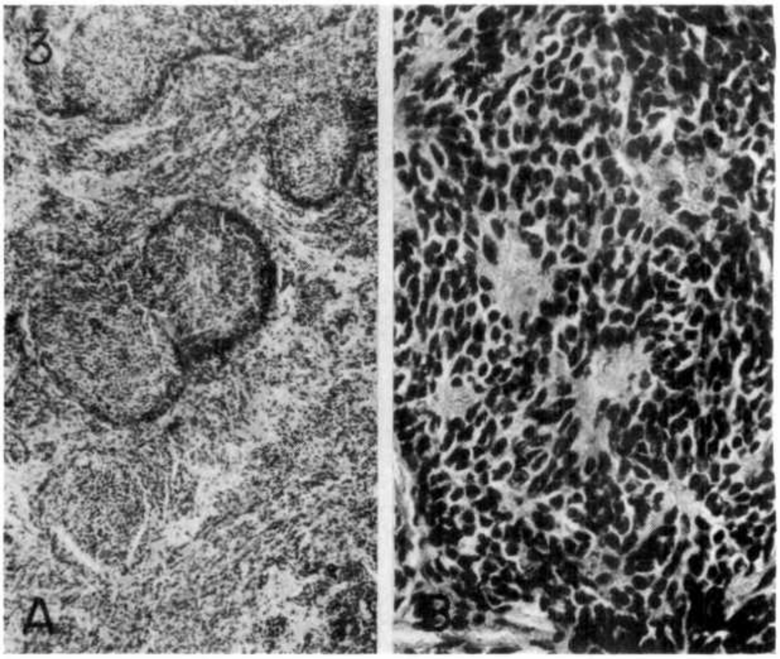

Fig. 3 *Microscopic features of tumour.* A: *Numerous small neoplastic cells in lobules and in no definite pattern of arrangement are shown (H–E, × 32).* B: *Homer Wright's rosettes are formed by primitive neuroepithelial tumour cells. Note tangles of cellular processes within the centre of rosettes (H–E, × 65).*

Microscopically, plentiful neoplastic cells of divergent types were found in lobules and in random distribution (Fig. 3A). Many small ovoid or carrot-shaped tumour cells with hyperchromatic nuclei rimmed by scant cytoplasm and hair-like cytoplasmic polar processes were often arrayed in rosettes that contained central tangles of these processes, representing Homer Wright's rosettes (Fig. 3B). These neoplastic cells were regarded as primitive (undifferentiated) neuroepithelial cells which resembled both neuroblasts and medulloblasts.

Several epithelium-like tumour cells had round to ovoid vesicular nuclei which were rimmed by homogeneous cytoplasm. Some had blue processes in PTAH preparations. They were occasionally arranged in true rosettes with central canals (Fig. 4A) and perivascular pseudorosettes characterised by attachment of the cellular processes to the vascular walls (Fig. 4B). These two patterns of the neoplasm were regarded as formed by ependymal cells.

A moderate number of the tumour cells had well defined outlines, distinctly clear perikaryon, and small dark nuclei giving a fried-egg appearance. They were interpreted as oligodendroglia (Figs. 4B, 5A). Neurons were not detected in Nissl's preparations.

A small number of widely scattered rounded tumour cells contained cytoplasmic GFAP and were regarded as neuroglia. Some had small dark nuclei surrounded by moderate amount of cytoplasm; they were interpreted as oligodendroglia (Fig. 5B). Others had large hyperchromatic nuclei rimmed by scant perikaryon; they were regarded as undifferentiated neuroglia (Fig. 5C). Similar GFAP-positive neuroglia, particularly astrocytes, were also seen in the fragment of normal brain serving as a control.

Reticulin fibres were few in some parts of the tumour but were numerous elsewhere (Fig. 6). This was also true for collagen fibres.

The pathological diagnosis was primary intraorbital, extraocular, primitive neuroectodermal tumour showing neuroglial differentiation and producing right proptosis.

POSTOPERATIVE COURSE

The patient received a course of radiotherapy totalling 5200 rad to the operative field over 1½ months. At the end of the radiotherapeutic course his vision was normal, as it was before the surgical intervention. The proptosis had improved, and the general condition was satisfactory. He was well when he was seen again 6 months later.

Discussion

The primitive neuroectodermal tumour is defined as a malignant neoplasm arising from primitive (stem cell) neuroepithelium which is capable of differentiating into various derivatives within the neuronal and neuroglial lines. Pathologically, Homer Wright's rosettes formed by primitive neuroepithelial cells are present. True rosettes and perivascular pseudorosettes may be present. The tumour may show a prominent mesenchymal component.[13]

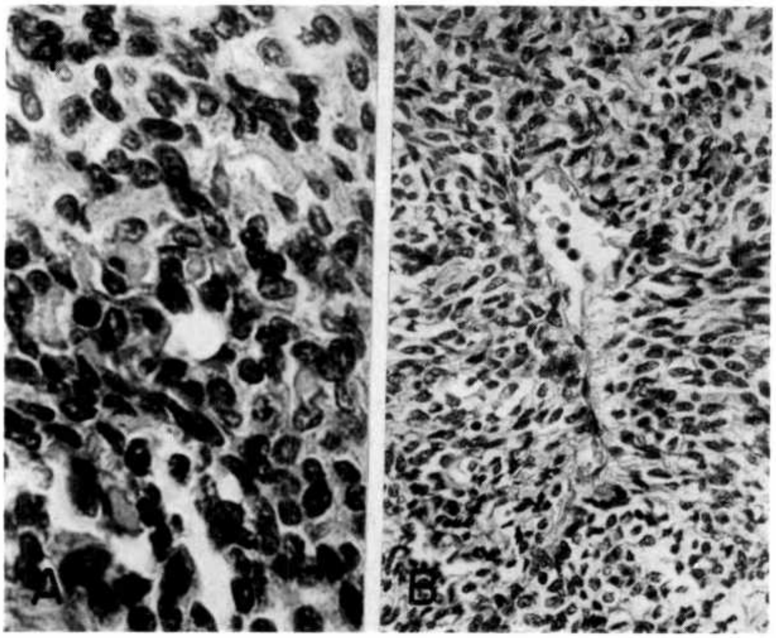

Fig. 4 *Ependymal and oligodendroglial differentiation of tumour.* A: *A true rosette formed by radially arranged ependymal tumour cells round central canal is shown (H–E, × 253).* B: *A perivascular pseudorosette consisting of central blood vessel with processes of ependymal tumour cells attached to its wall is shown. Some rounded neoplastic cells having distinctly clear perikaryon round small nuclei to give fried-egg appearance, as in a cluster at the right lower corner of the photomicrograph, are considered to be oligodendroglia (H–E, × 63).*

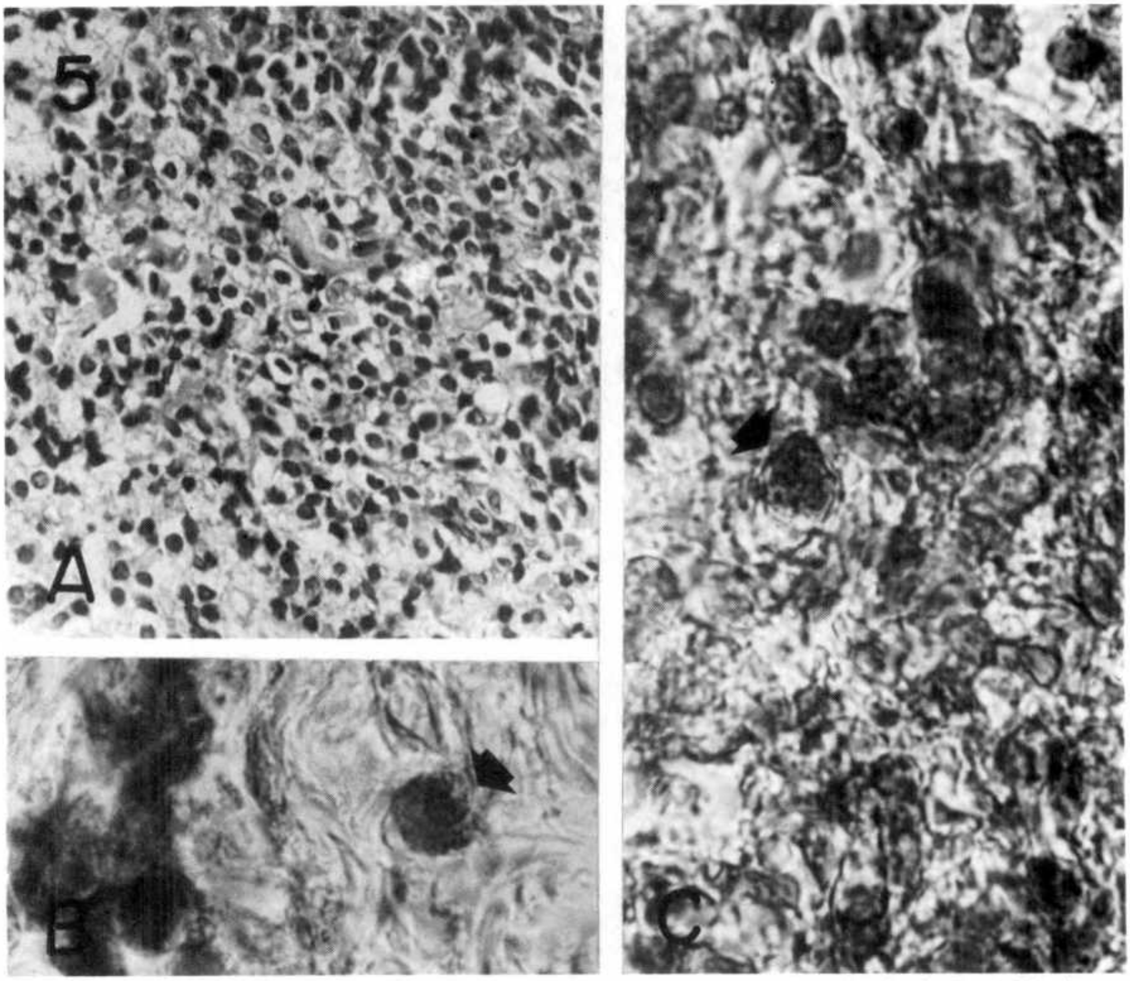

Fig.5 *Oligodendroglial differentiation and result of immunohistochemical study.* A: *Many oligodendroglia with fried-egg appearance are shown (H–E, × 100).* B: *A GFAP-positive tumour cell interpreted as oligodendrocyte (arrow) is demonstrated (GFAP stain, × 1000).* C: *A neoplastic cell having large hyperchromatic nucleus surrounded by scant GFAP-positive perikaryon regarded as undifferentiated neuroglial cell (arrow) is present among other undifferentiated tumour cells (GFAP stain, × 1000).*

The intraorbital extraocular neoplasm described here fulfils these criteria for designating it as a primitive neuroectodermal tumour because it had primitive neuroepithelial cells forming Homer Wright's rosettes, ependymal cells forming true rosettes and perivascular pseudorosettes, and neoplastic oligodendroglia. The present of neuroglia within the tumour was confirmed by the localisation of cytoplasmic GFAP in some tumour cells, as we have demonstrated previously.[6-9] In those studies all kinds of neuroglia (astrocytes, ependymal cells, oligodendroglia, and undifferentiated neuroglia) were GFAP-positive.[6-9]

Nevertheless, the presence of primitive neuroepithelial cells forming Homer Wright's rosettes in the present tumour suggests that it is a neuroblastoma. Indeed, neuroblastomas in adult patients have been reported.[10] However, the concept of the primitive neuroectodermal tumour encompasses as well the neuroblastomas. A neuroblastoma can be perceived as primitive neuroectodermal tumour with entire neuroblastic differentiation. The present intraorbital extraocular neoplasm is a primitive neuroectodermal tumour with neuroglial differentiation. Nevertheless a small number of GFAP-positive neuroglial neoplastic cells as well as prominent reticulin and collagen fibres in some parts of this tumour may not support the diagnosis of the primitive

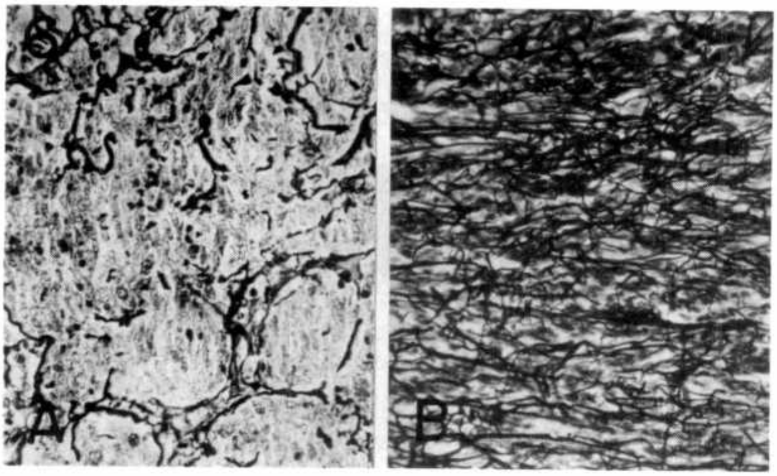

Fig. 6 *Reticulin fibres within tumour.* A: *Few reticulin fibres are present around some lobules of the tumour cells but are absent within lobules (Gomori's stain, × 72).* B: *Dense reticulin fibres are shown in a field of less numerous neoplastic cells (Gomori's stain, × 72).*

neuroectodermal tumour but favour a mesenchymal origin of the neoplasm. According to our experience, however, ependymal and oligodendroglial tumour cells are not frequently GFAP-positive, as are astrocytes, which were not seen in the present tumour. A prominent mesenchymal component is known in primitive neuroectodermal neoplasms.[1]

We regard the current primary intraorbital, extraocular, primitive neuroectodermal tumour as akin to those neoplasms reported as neuraxial primitive neuroectodermal tumours, including the cerebellar medulloblastomas[1,3,11] and to some peripheral nerve neoplasms which have been described as malignant neuroepitheliomas,[12-14] malignant ependymoma,[15] and primitive neuroectodermal tumour (neuroblastoma).[5] These peripheral nerve tumours contained Homer Wright's rosettes and true rosettes as in our patient's tumour relating to the orbit. They often metastasised widely.[5,12-15]

The primitive (stem cell) neuroepithelium has been suggested as the origin of the neuraxial primitive neuroctodermal tumours.[3,11] For the peripheral primitive neuroectodermal tumours an origin from the neural crest has been proposed.[9] Evidence has been presented relating to the combined mesenchymal and neuroectodermal (ectomesenchymal) nature of the neural crest,[9,16-18] because it is formed by mingling of the mesenchyme and developing neuroepithelium of the neural folds before closure of the neural tube.[17] The neural crest yields diverse derivatives of both mesenchymal and neuroepithelial lines which migrate throughout the body, particularly in association with the peripheral nerves.[19] Although no connection of the present tumour with any major nerve was observed clinically, its origin from a small nerve, such as a nerve twig, cannot be excluded. Moreover, in the development of the eyeball, which has been reviewed previously,[20] the primitive neuroepithelium forming the optic primordium may become ectopic within the orbit, a comparable developmental anomaly known as heterotopia of the neuraxis.[8,21] This heterotopic neural tissue and/or neuroectodermal component of the neural crest comprising the sheath of the peripheral nerve within the right orbit may be the origin of our patients tumour, which further differentiated into diverse neuroepithelial derivatives.

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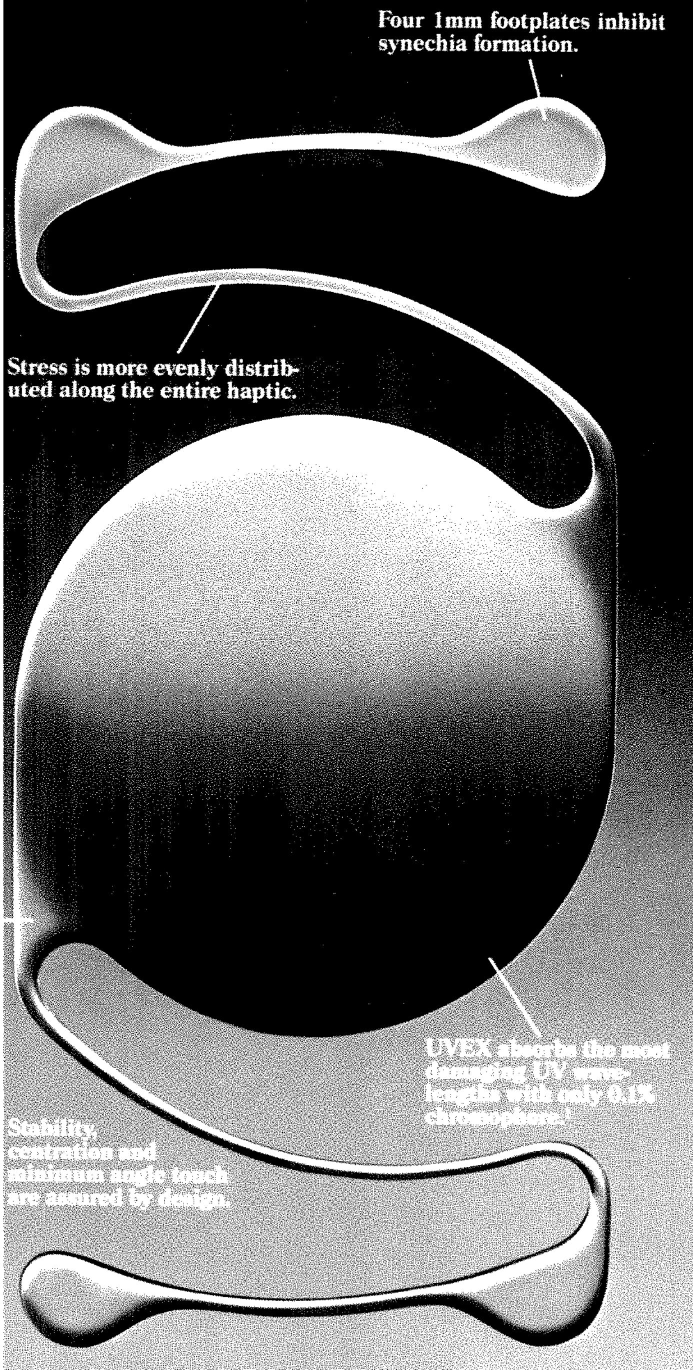
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British Journal of Ophthalmology, 1986, **70**, 549–552

The magician's forceps phenomenon in exotropia under general anaesthesia*

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SUMMARY Prifinium bromide was administered for eight weeks to three patients with exotropia. Under general anaesthesia active discharges from the lateral rectus muscles were demonstrated by electromyography. When a slight adductive force was applied to the straight or the master eye, active discharge from the lateral rectus of the associate eye disappeared in all patients, and this eye moved in the direction of orthophorisation. The discharge reappeared when the master eye was released from the forced adduction. From these results the authors concluded that proprioception is involved in the magician's forceps phenomenon discovered by Mitsui in exotropic patients in 1978.

The magician's forceps phenomenon is the orthophorisation of exotropia when a slight adductive force is applied to the straight, or master, eye. It was first reported by Mitsui in 1978.[1] This phenomenon is characterised by monocular movement of the slave eye in the direction of orthophorisation, as shown by electromyography.[2] Once the phenomenon appears, it does not disappear when the master eye is covered, even in cases in which the slave eye has no sight,[2,3] and the reflex responds to 9 Hz forced adduction.[3] These facts suggested the involvement of proprioception in the phenomenon. However, the phenomenon does not appear during forced adduction,[2] so that the importance of visual input has also been stressed.[2,3] Therefore it was supposed that the development of the phenomenon[4] was due to an interaction between the proprioceptive and visual afferents. This supposition was also suggested by the results of a series of basic studies on animals.[5-7]

Recently Tamura and Mitsui[7] studied the optomotor effect and the effect of retrobulbar anaesthesia in exotropic patients using electromyography after treatment with prifinium bromide, when there was active discharge from the lateral recti under general anaesthesia. The results strongly suggested that an interaction between the proprioceptive and visual afferents is involved in the firing from the lateral recti.

The present study was performed on exotropic patients treated with prifinium to determine whether or not forced adduction of the master eye causes the magician's forceps phenomenon under general anaesthesia, and thus to prove the presence of a stretch reflex in extraocular muscles.

Materials and methods

Three patients of constant exotropia, two males and a female ranging in age from 8 to 34 years, were given prifinium bromide for eight weeks in the manner reported previously.[7] Electromyograms (EMGs) of the four horizontal rectus muscles were taken under general anaesthesia as in the method described earlier.[8] In all three patients active discharges were emitted from both lateral recti, or at least from the lateral rectus of the slave eye. A slight adductive force was then applied to the straight, or master, eye by pulling a silk thread inserted at the medial limbus. The forced adduction was continued for two minutes. The experiment was done under the illumination with skialytic light.

All experiments were performed with the informed consent of the patients.

Results

The magician's forceps phenomenon, as revealed by EMGs, occurred in all the three patients examined

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*Read in part before the 5th meeting of the International Neuro-ophthalmology Society, Antwerp, 14–18 May 1984.

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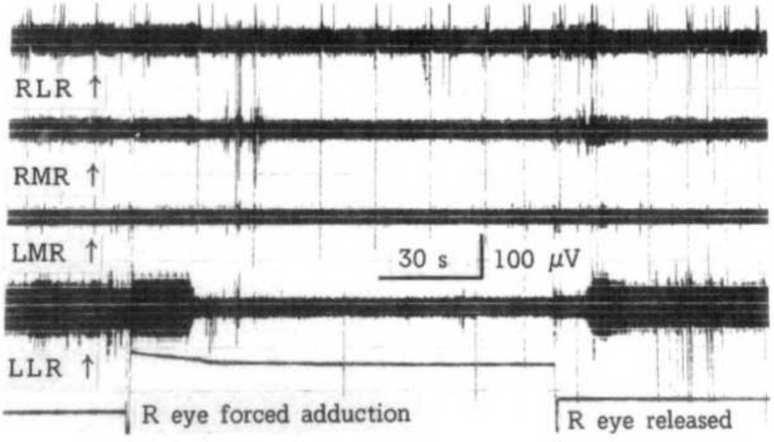

Fig. 1 *EMGs showing the magician's forceps phenomenon under general anaesthesia in a patient with exotropia of the left eye treated with prifinium. Discharge from the left (slave) lateral rectus tapers off when forced adduction is applied to the right (master) eye, and reappears when this eye is released from forced adduction.*

under general anaesthesia. Examples are shown in Figs. 1 and 2A, B.

Fig. 1 shows the EMGs obtained from a 23-year-old male suffering from constant exotropia of the left eye. The deviation was 28°, and vision was 20/20 in both eyes. When prifinium bromide was administered orally for eight weeks, at a dosage of 15 mg three times a day, the deviation became slightly greater. Under general anaesthesia the deviation was seen mostly in the left eye. The EMGs revealed a considerable amount of active discharge from the left lateral rectus. When a slight forced adduction was applied to the right, or master, eye, active discharge from the lateral rectus of the left, or slave, eye disappeared 16 to 19 seconds after application. The forced adduction was maintained for two minutes and then the right eye was released. Active discharge from the left lateral rectus reappeared about eight seconds after release of adduction. The horizontal recti of the right eye showed little change throughout.

Figs. 2A, B show EMGs obtained from a 15-year-old girl suffering from constant exotropia of the left eye. The deviation was 25°, and vision was 20/20 in the right and 20/100 in the left eye with no organic changes (amblyopia). The deviation became slightly greater when prifinium bromide was administered at a dosage of 45 mg a day for eight weeks. Under general anaesthesia both eyes showed a 'symmetrical exodeviation,' and active discharges were seen from both lateral recti (Fig. 2A). When a slight forced adduction was applied to the right (master) eye, active discharge from the left (slave) lateral rectus disappeared 24 to 34 seconds later. At the same time active discharge appeared from the medial rectus of the same eye. When the master eye was released from the forced adduction, active discharge from the slave medial rectus disappeared in 7 to 15 seconds accompanied by the reappearance of active discharge from the lateral rectus of the same eye in the course of 30 to 35 seconds, so that the EMGs returned to the original pattern. No obvious changes were seen in the EMGs of the right (master) eye muscles to which the forced adduction was applied.

When the same procedure was repeated twice, as shown in Fig. 2B, changes similar to those observed in the first attempt appeared in the EMG of the left lateral rectus but no changes appeared in the medial rectus.

In each case movement of the slave eye in the direction of orthophorisation appeared insidiously after a long time lag during forced adduction to the master eye.

Discussion

The present experiment showed that the magician's forceps phenomenon occurs under general anaesthesia. The indispensability of visual input for the transmission of proprioceptive afferents from ocular muscles had been suggested by a series of investigations.[2-7, 9] The present experiment was therefore done in the light. Under general anaesthesia the slip of the retinal image has nothing to do with the ocular movement, so that the present result must be considered to be due to the stretch reflex transmitted through a subcortical pathway, most probably after an interaction with the visual afferent.

Ishikawa[10] showed that in conscious patients the reverse phase reflex[11] can be brought about by forced duction of the excited eye by the use of a black suction contact lens, but there is a time lag of about seven seconds, and in addition the reflex appears only when the slave eye is also covered by a black contact lens.

It is not surprising, therefore, that in the experiment by Keller and Robinson[12] the stretch reflex did

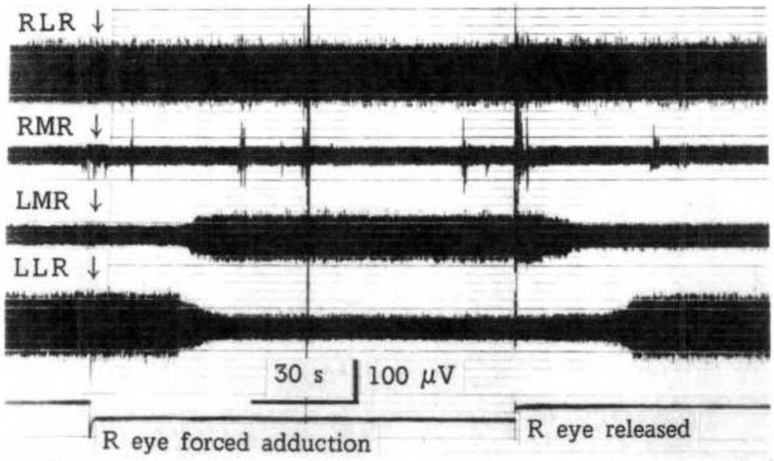

Fig. 2A

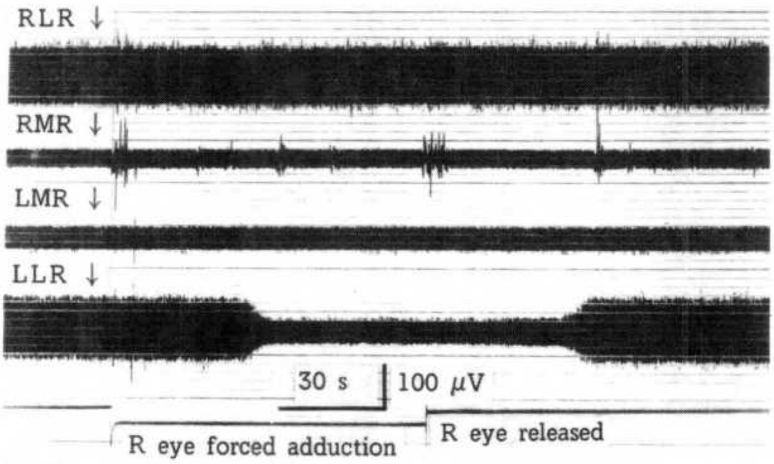

Fig. 2B

Fig. 2 *EMGs showing the magician's forceps phenomenon under general anaesthesia in another patient with exotropia of the left eye treated with prifinium.* A: *By forced adduction of the right (master) eye, there is disappearance of discharge from the left (slave) lateral rectus accompanied by an increase of discharge from the medial rectus of the same eye, and EMGs return to the original pattern by release from forced adduction of the right eye.* B: *As above, but not accompanied by an increase in discharge from the medial rectus, obtained by repeated attempts in the same patient.*

not appear in the EMG, because they covered the eye to which the forced duction was given while the associate eye was opened and the forced duction was given only 300 ms. However, the experiments by Breinin[13] and Maruo[14] showed a positive stretch reflex by EMG. Another reason for the negative result reported by Keller and Robinson may be due to the fact that they measured the reflex in the ipsilateral lateral rectus. Our series of studies have shown that the reflex is chiefly transmitted to the contralateral lateral rectus.

The magician's forceps phenomenon is a monocular movement of the slave eye in the direction of orthophorisation when studied by EMGs in conscious patients.[2] This phenomenon in conscious patients is of two types.[2,3] In one the slave eye assumes a position slightly off the straight position, and in the other the slave eye assumes the straight position, when a slight adductive force is applied to the master eye. In both types the EMGs show a tapering off of abnormal discharge from the lateral rectus of the slave eye accompanied by an increase in the discharge of the medial rectus. However, in the first type of response the EMGs of the medial and lateral rectus muscles are finely balanced, whereas in the second type dominance of the medial rectus appears. These two types are not person-specific, and either may appear in the same patient during repetition of the attempts. The present experiment showed that in the magician's forceps phenomenon under general anaesthesia equivalents to these two types can also appear in EMGs. The only difference is the length of the time lag under general anaesthesia.

The optomotor effect under general anaesthesia appears after long time lags.[7,9] The stretch reflex shows the same delay under general anaesthesia. In addition, darkness and stretching show the same effect in the same pattern on the EMGs of exotropia. These facts may contribute to our further understanding of the mechanism of interaction between the visual and muscle afferents.

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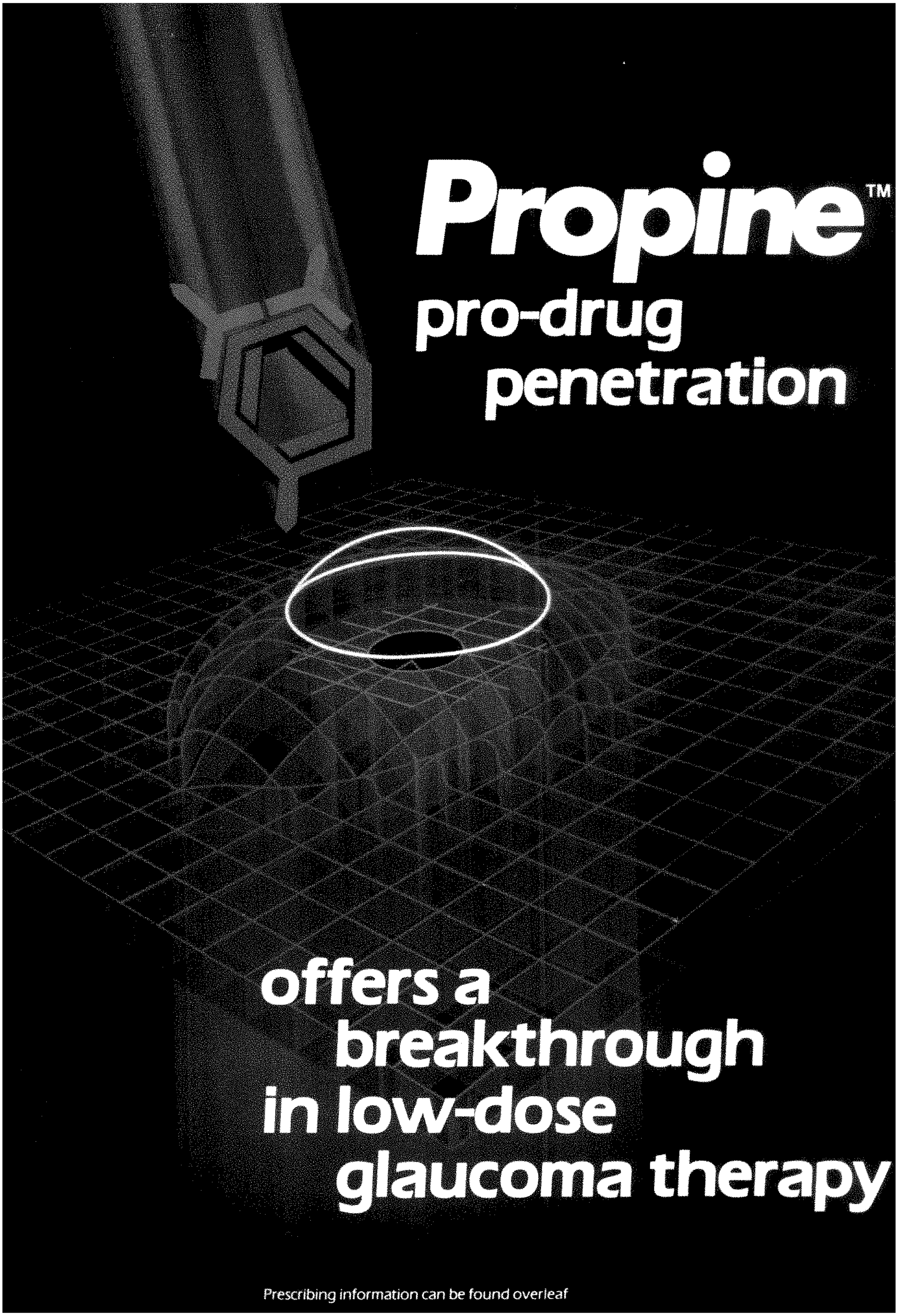

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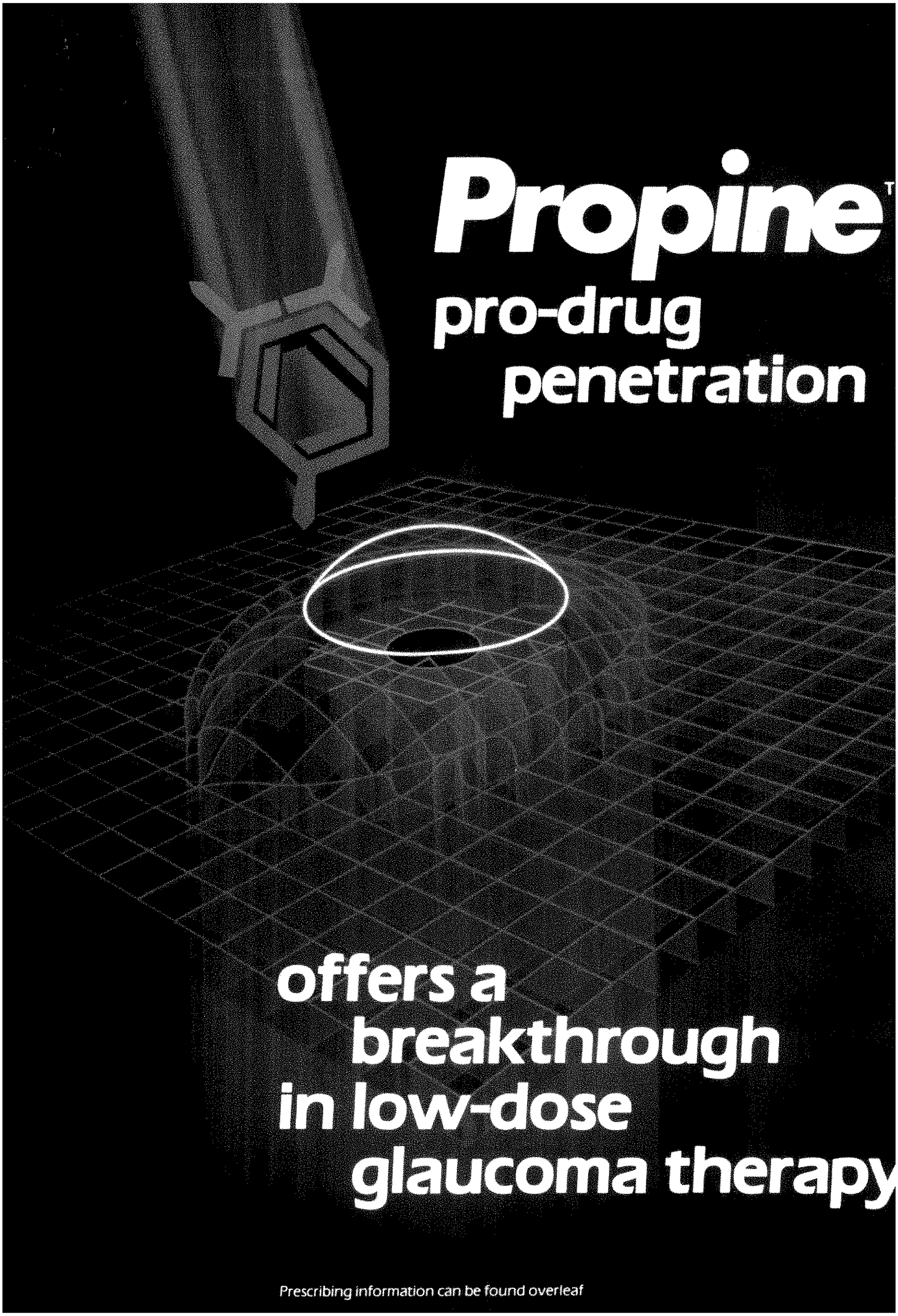

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British Journal of Ophthalmology, 1986, **70**, 553–559

Contrast sensitivity versus visual acuity in retinal disease

MICHAEL F MARMOR

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SUMMARY A large group of individuals with retinal disease were tested prospectively for contrast sensitivity by means of Arden gratings. A subgroup of 19 were also tested with the Nicolet automated television system. Individuals with macular or peripheral dystrophy showed a general reduction in contrast sensitivity as visual acuity decreased. The loss of contrast sensitivity was more prominent for high spatial frequencies (6·4 cycles per degree) than for low ones (0·2 cycles per degree). Similar results were obtained for patients with achromatopsia and congenital stationary night blindness. Patients with functional complaints, but no organic basis for decreased acuity, showed greater scatter in their test scores. The Nicolet results showed somewhat smoother curves, but were no more specific in separating normality from abnormality. Contrast sensitivity testing was not specific for the retinal disease entities considered, but may be useful in recording a degree of retinal damage and a degree of functional visual disability. Contrast sensitivity appeared to be reduced whenever acuity was reduced, so that a distinction could be made between patients having a loss of contrast beyond the expectations for their level of acuity and those in whom a loss of contrast simply corroborates the reduction of acuity.

Snellen visual acuity testing is a relatively crude index of visual function, in so far as it measures resolution only with high contrast targets, since objects in the real world exhibit varying degrees of contrast and a varying content of spatial frequencies. There has been considerable interest in recent years in developing practical clinical tests for contrast sensitivity. Several systems are now commercially available, including a set of printed plates,[1 2] a computerised television system,[3] and a set of posters.[4] Reports have appeared showing that contrast sensitivity deficits out of proportion to visual acuity may be found in patients with retinal or optic nerve disease.[2 5-10] There have been no large series published, however, to show the incidence of contrast sensitivity defects in macular or retinal disease, or to show whether the pattern of loss has diagnostic or prognostic value. There is also little information on what levels of contrast deficit to expect simply on the basis of decreased acuity. The present study shows the result of prospective contrast sensitivity testing with Arden gratings on a large group of patients and on a subgroup with the Nicolet television system.

Material and methods

Over a two-year period all patients referred for clinical visual electrophysiological testing at the Stanford University Medical Center were given the Arden grating test. All testing was performed by a single examiner, who followed the technique of Arden *et al.*[1 2] Each grating was covered with a sheet of grey paper that was slowly removed, exposing progressively higher levels of contrast. The six vertical sinusoidal gratings (numbered 2–7) have spatial frequencies of 0·2, 0·4, 0·8, 1·6, 3·2, and 6·4 cycles per degree (cpd) respectively. Marginal numbers range from 0 at the low contrast end to 20 at the high contrast end; a score of 25 is assigned arbitrarily if the subject is unable to perceive the grating.

For a period of three months we had use of an Optronix 2000 contrast sensitivity test system, courtesy of Nicolet Instrument Company. We programmed this system to mimic the Arden test protocol: gratings of 0·5, 1·5, 3·0, and 5·71 cpd were

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presented by the 'method of increasing contrast', which requires the observer to push a button when the grating first becomes visible. The pattern was presented four times at each spatial frequency.

We have tabulated data from subjects who fit into several major diagnostic categories. 'Normals' were 16 persons aged 10–33 with 20/20 acuity, no symptoms, and no evidence of ocular disease; most of them were unaffected family members of patients with disease. Patients with 'macular dystrophy' (n=50), aged 6–76, included some with Stargardt's disease, Best's vitelliform dystrophy, and patients with unclassified bilateral maculopathy that could not be ascribed to infectious, degenerative, or other secondary causes. Patients with 'diffuse dystrophy' (n=61, ages 6–66) include those with retinitis pigmentosa and its variants, as well as unclassified conditions in which there was bilateral diffuse retinal damage noted by ERG or fundus examination, and no evidence for an acquired aetiology. Specifically excluded from this group are carriers of X-linked retinitis pigmentosa, individuals with mild or 'delimited' forms of retinitis pigmentosa,[11] and patients with predominantly cone or central dystrophies. Patients with achromatopsia (n=6, ages 10–34) and congenital stationary night blindness (n=7, ages 8–47) were classified on the basis of ERGs that showed an absence of cone or rod function respectively, and had histories and physical findings consistent with stationary congenital disease. Patients with 'functional complaints' (n=19, ages 8–66) had visual symptoms that could not be substantiated by physical findings.

Snellen visual acuities were tested with a conventional clinical projection system using the subjects' best known correction. However, many of the subjects were referred only for electrophysiological testing, and the accuracy of their refraction was not confirmed.

Results

Arden grating scores for normal subjects (one eye only) with 20/20 vision were close to Arden's values.[1] The total score (sum of all six gratings) averaged 65·0±6·8 (standard deviation). Despite the manual technique for unmasking the gratings, Arden scores were remarkably consistent. Four patients with stable disease had repeat testing at intervals between 7 and 21 months, and their total scores did not vary more than 10%.

Fig. 1 shows data from all eyes with macular dystrophy. The total Arden grating scores (top) generally increased as visual acuity decreased, although a wide range of total scores are evident even among those eyes with good acuity (20/40 or better).

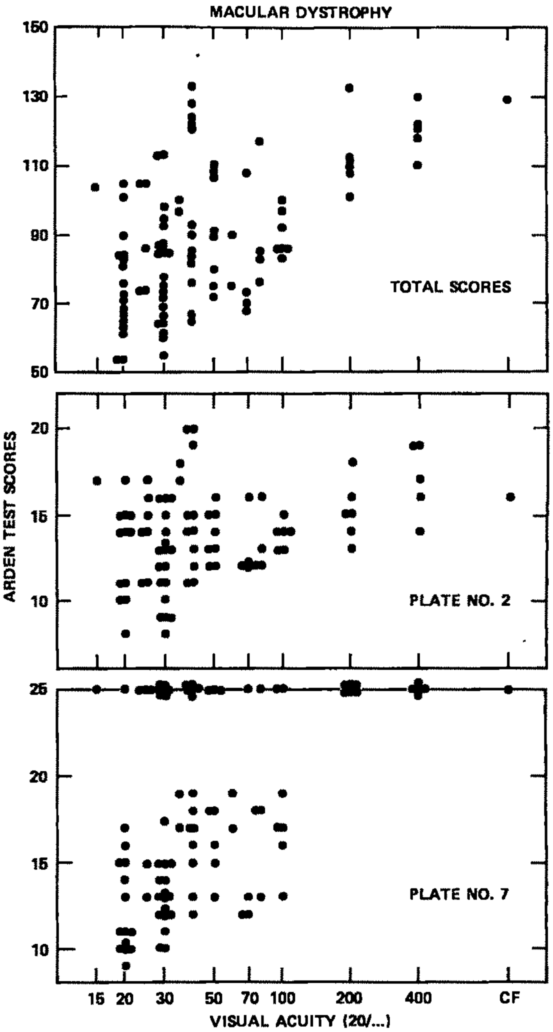

Fig. 1 *Arden grating scores from eyes with macular dystrophy. The data are plotted against a logarithmic scale of visual acuity.* Top: *Total scores.* Middle: *Scores on plate number 2 (0·2 cpd).* Bottom: *Scores on plate number 7 (6·4 cpd).*

The middle and bottom parts of Fig. 2 show scores from the coarsest (0·2 cpd) and finest (6·4 cpd) gratings respectively. All of the eyes with macular dystrophy could perceive the coarse grating, but a significant number of eyes could not appreciate the finest grating (scores of 25) even though acuity was excellent.

Similar results were obtained from patients with diffuse dystrophies (Fig. 2).

Fig. 3 shows the results from patients with achromatopsia and congenital stationary night blindness (CSNB), both non-progressive disorders of retinal

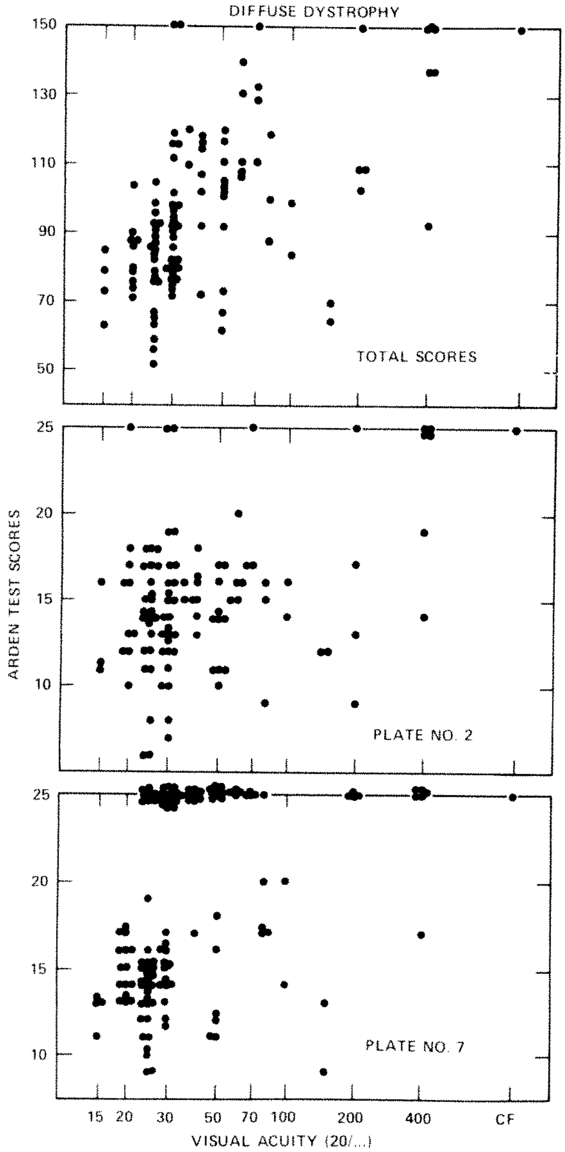

Fig. 2 *Arden grating scores from eyes with diffuse dystrophy, presented as in Fig. 1.*

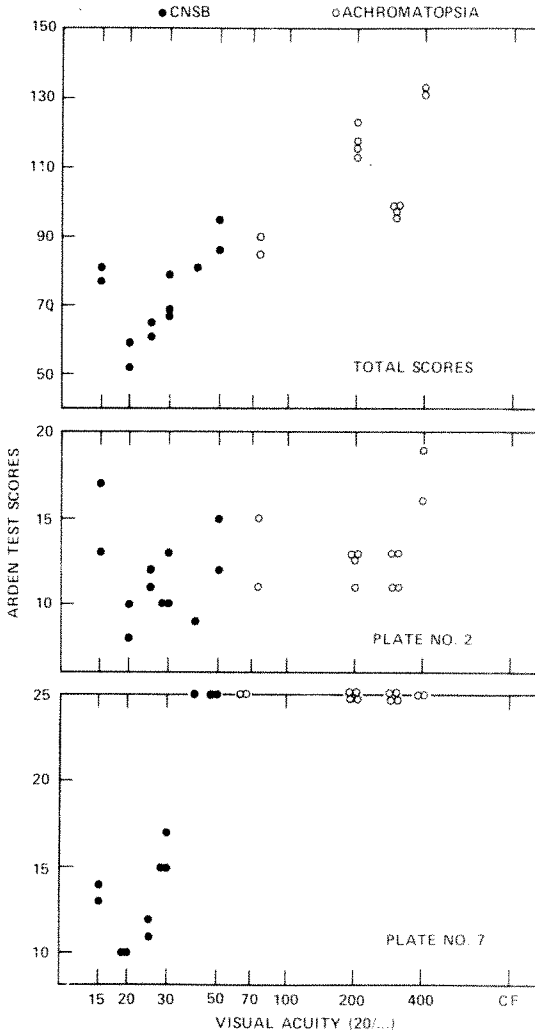

Fig. 3 *Arden grating scores for eyes with achromatopsia (○) and congenital stationary night blindness (●), presented as in Fig. 1.*

function. The total scores generally correlated with the levels of acuity in these subjects. All subjects perceived the coarsest grating, but those with reduced acuity could not perceive the finest one.

The patients with 'functional complaints' (Fig. 4) had a range of symptoms including poor acuity, sensitivity to glare, poor dark adaptation, and field constriction, but they showed no clear fundus abnormalities and had normal electrophysiological test results. The total grating scores for their eyes tended to increase as visual acuity decreased (with the exception of two questionably low scores in a patien who tested at 20/70 acuity), but the scatter was more pronounced and less predictable for each individua grating.

Fig. 5 compares results obtained with Arden gratings with those obtained with the Nicolet unit at similar spatial frequencies and with a similar test protocol (method of increasing contrast). Because of the different clinical scoring methods the best performances shown in Fig. 5 lie near the bottom of the Arden graphs but near the top of the Nicolet graphs. We did not have the opportunity to obtain normative control data for the Nicolet unit, and the 'normal'

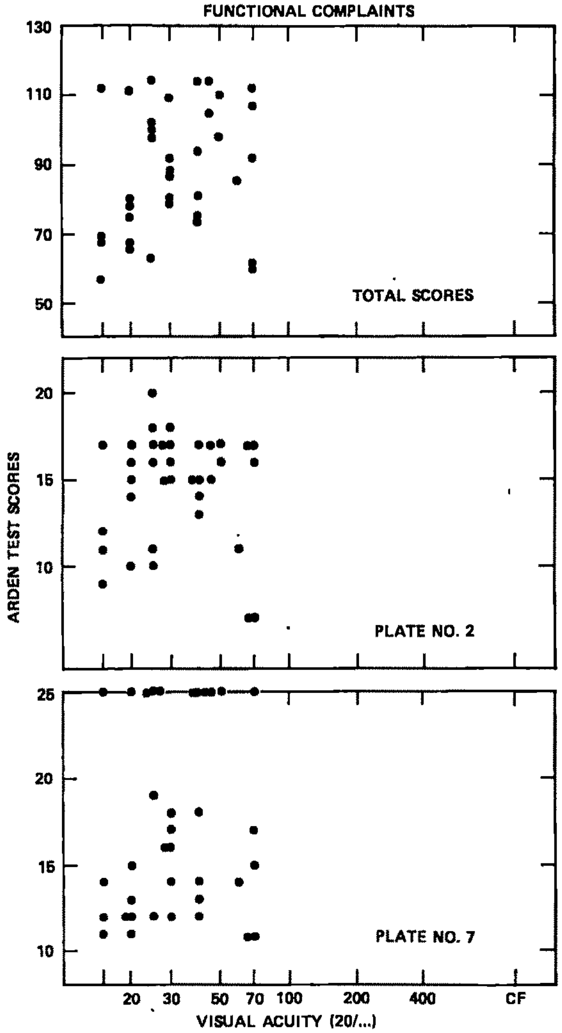

Fig. 4 *Arden grating scores for patients with functional visual complaints but no demonstrable organic disease.*

values shown were copied from the literature.[3] They may well be too high, since they were obtained using the von Bekesy test protocol, which tends to yield higher sensitivity values than the method of increasing contrast.[12]

Of the subjects with macular dystrophy (Fig. 5, top), those with relatively good acuity showed relatively normal contrast sensitivity functions, measured by either system. Since the true range of normal for the Nicolet results is probably lower than illustrated, it may well incorporate all of the top four curves in the upper right panel. The two individuals (■, △) with very poor contrast sensitivity (visual acuities 20/60, 20/100) were abnormal by both tests. There was somewhat greater scatter of data with the Arden gratings, but the Arden gratings also identified some abnormal responses to (e.g., to 6·4 cpd for subjects ● and ○) that were not clearly evident on the Nicolet testing. The patients with diffuse dystrophy (Fig. 5, middle) showed, by either technique, a greater loss of high than low frequency sensitivity. The Arden results showed a severely abnormal contrast sensitivity for four of the six eyes, whereas only three of the six were severely abnormal by Nicolet testing. The patients with functional complaints (Fig. 5, bottom) showed considerable scatter in their Arden results and had scores that sometimes fell in the borderline or elevated range. On testing with the Nicolet unit they showed more consistent curves, with predominant loss of sensitivity at higher frequencies.

Discussion

These data show clearly that contrast sensitivity is often subnormal in patients with retinal disease who still have relatively good acuity as measured on the Snellen chart. Conversely, some eyes with reduced central vision may show surprisingly good contrast sensitivity, especially for gratings of low spatial frequency. These general conclusions are consistent with earlier studies[5-10] and show as well that patterns of contrast deficiency are not very specific to one or another type of ocular pathology. For all of the retinal diseases tested the contrast sensitivity loss was most severe at higher spatial frequencies, and low frequencies were rarely compromised unless there was also a severe loss of visual acuity. The patients with functional complaints showed a scatter of data on contrast sensitivity testing, but this is consistent with their variable performance on other subjective tests.

These results do not mean that contrast sensitivity testing is of no value, of course. Contrast sensitivity testing may detect early organic damage before acuity is compromised; it may also help to follow (with coarse gratings) the progression of severe disease when acuity is already at a low level. Furthermore, the assessment of functional disability gives us understanding of how well adapted or badly adapted our patients are to visual tasks in the real world.

The Arden gratings have been criticised because of the manual procedure for uncovering the gratings. Arden[12] has claimed that the errors produced by operator variability are relatively minor, and this was our experience as well. The automated Nicolet system produced smoother curves than the Arden plates, but it did not appear any easier to separate normality from abnormality with the Nicolet data.

This study points out the importance of interpreting

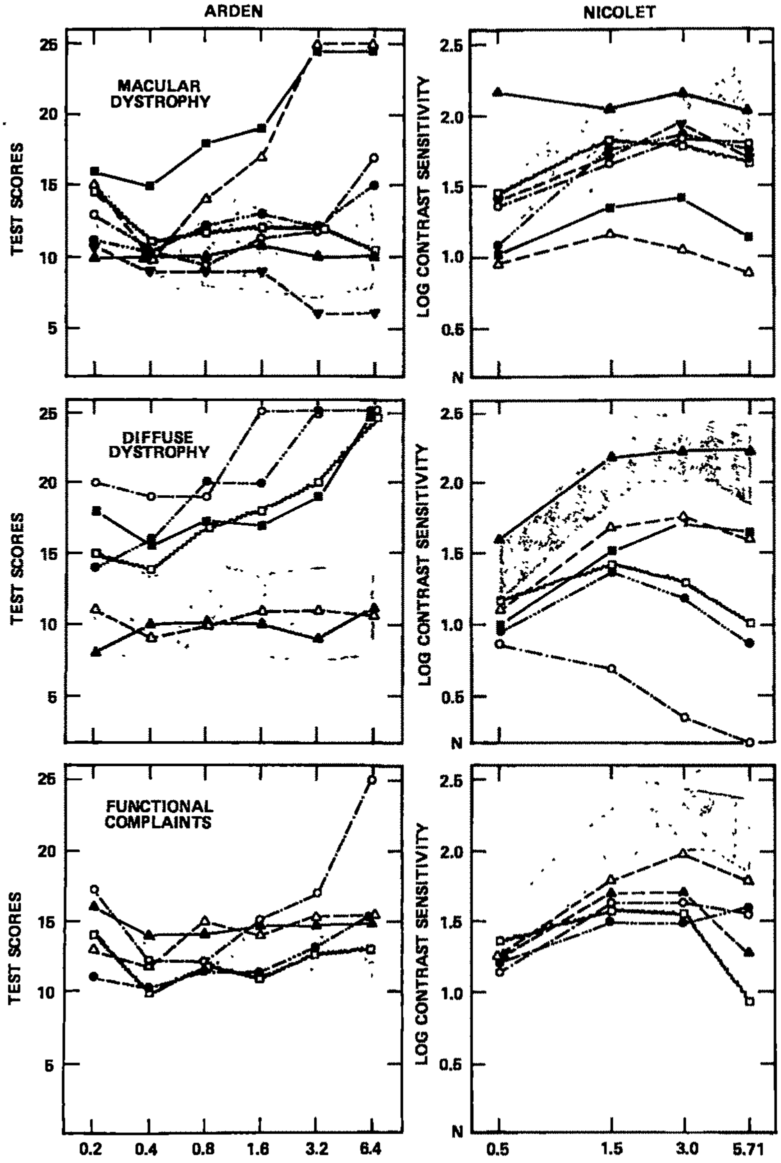

Fig. 5 *Comparison between Arden and Nicolet contrast sensitivity scores for eyes with macular dystrophy* (top), *diffuse dystrophy* (middle), *and functional complaints* (bottom). *The range of normal values (mean±2 standard deviations) is shown for each test, but may be high for the Nicolet unit (see text). Each symbol represents a separate patient. Note that good performance is indicated by* low *Arden scores but* high *Nicolet scores.*

contrast sensitivity within the context of visual acuity. Note in Figs. 1–4 that for each disease category even the best recorded total Arden scores increase with acuity in a remarkably linear fashion. This relationship is seen to a lesser degree in the scores for individual gratings. The nature of this covariance is shown better in Fig. 6. The straight line C represents the best actual scores achieved by our subjects at different levels of acuity: it extends from 2 standard deviations below the 20/20 mean to a score of 150 at a hypothetical acuity of 20/6400*. For comparison line D represents a theoretical limit beyond which no score can go: it begins near 20/100 where the spatial resolution (visual angle=5′) approximates that of the

---

*Snellen acuity of 20/20 is defined as the ability to resolve letters of 1′ visual angle; thus, an acuity of 20/100 should be near the optical limit to perceive a grating of 5′ per band, which is close to the spatial frequency of plate 7 (6·4 cpd). Indeed, our data show that some subjects with 20/100 could perceive the plate 7 grating, but none with 20/200 were able to perceive it. By extension 20/400 eyes would miss 3·2 cpd gratings, etc., and subjects with '20/6400' acuity would be unable to resolve plate 2 (0·2 cpd) and would therefore miss *all* the plates.

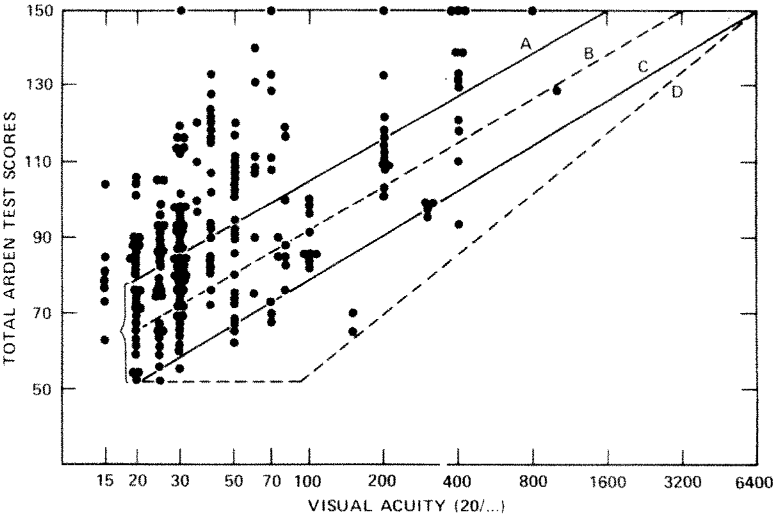

Fig. 6 *Composite plot of all total Arden scores versus visual acuity. The parallel lines* A, B, *and* C *intersect 20/20 acuity at the mean score for normal subjects* ±2 *standard deviations. Line* D *corresponds to the theoretical 'best' scores if reduced acuity affected only the perception of gratings at the limit of resolution. See text.*

finest Arden grating (6·4 cpd). Any patient with a total score less than line D must be either anticipating the appearance of the gratings or responding falsely.

Fig. 7 demonstrates that contrast sensitivity falls progressively with decreasing acuity, even for gratings whose spatial frequency is well within the subject's powers of resolution. For example, the 'best' score for 6·4 cpd plate 6 rises with even small losses of resolution (eg., 20/30 and 20/40) that do not come close to compromising perception of the grating. Similarly, when acuity is reduced to 20/200, the scores are elevated for all six plates even though the coarser gratings can still be easily resolved. This suggests that individuals with acuity less than 20/20 may be *expected* to show elevated Arden scores on the basis of their acuity alone, independently of other pathological concomitants. Only if the contrast deficit exceeds the normal (±2 SD) range that one would expect on the basis of acuity (i.e., the scores are above line A) can we conclude that contrast sensitivity is specifically or preferentially damaged. Contrast sensitivity better than expected on the basis of acuity (i.e., scores below line C) should raise doubts about the reliability or credibility of the subject. Table 1 lists these upper and lower Arden score limits for various levels of visual acuity. Similar graphs and tables could be constructed of course for data from other contrast sensitivity test systems.

This method of analysis has not, to my knowledge, been presented previously, though other studies have skirted some of the issues. Arden[1] pointed out that mild refractive errors affect only higher spatial frequencies, but he did not report results for a range of acuities. Skalka[6] plotted some of his data in the same way as ours but did not explore the implications. Campbell and Green[13] showed effects similar to those in Fig. 7 for a range of different refractive errors, and Hess[14] reported different patterns of contrast loss with different causes of poor acuity. But close

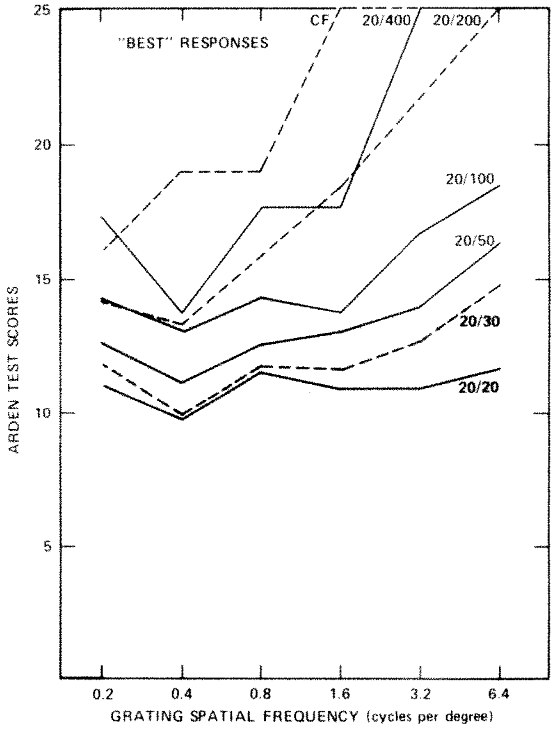

Fig. 7 *Individual Arden grating scores averaged from the 'best' eyes at each level of visual acuity (eyes whose total scores fell between lines* A *and* C *in Fig. 6). The range of values for normal subjects with 20/20 acuity is shown* ±2 *standard deviations.*

Table 1 *Arden norms in relation to visual acuity*

Visual acuity	*Total Arden scores**		
	−2 SD	*Average*	*+2 SD*
20/20	51	65	78
20/25	55	69	82
20/30	58	72	85
20/40	63	77	90
20/50	67	80	93
20/70	73	86	99
20/80	75	88	101
20/100	79	92	105
20/200	91	104	116
20/400	102	115	127
CF	118	131	142

*Data derived from Fig. 6. Scores below −2 SD are 'too good' and should be questioned. Scores above +2 SD are pathological beyond the usual relationship to reduce acuity. SD=standard deviation.

comparison with either of these sets of data is difficult because the authors did not report the associated levels of visual acuity. Bodis-Wollner[15] stated that acuity alone does not predict the pattern of contrast loss. Our data confirm that statement in so far as the more pathological scores are concerned, but our data also suggest that acuity does predict a baseline or 'best' level of contrast sensitivity.

One may criticise our conclusions because the data are derived from subjects with retinal or functional disease rather than from individuals with purely refractive loss of acuity. However, in view of the diversity of diagnoses and the spread of results in this study it does not seem unreasonable to postulate that the very best subjects at each level of acuity had contrast sensitivity scores near the optimum possible (regardless of whether the visual loss was retinal or refractive).

These results are relevant to the clinical application of contrast sensitivity testing. To the extent that a patient's low contrast sensitivity scores reflect only visual acuity, they add little to our diagnostic acumen; in fact they may give a misleading impression of specific pathology. If acuity effects are taken into account, then contrast sensitivity deficits beyond the level accounted for by acuity may have greater significance than previously appreciated.

Supported in part by National Eye Institute Grant EY 01678, the Medical Research Service of the Veterans Administration, and Research to Prevent Blindness, Inc. I thank Dr W J Donovan for helpful comments on the manuscript.

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British Journal of Ophthalmology, 1986, **70**, 560

Book reviews

Common Eye Diseases and their Management. By N R GALLOWAY. Pp. 278. £27·25. Springer-Verlag: Berlin. 1985.

This must surely be the easiest-to-read textbook of ophthalmology in publication. The clearly written text is very suitable for the readership it is intended for, namely medical students and colleagues in other specialties.

The author first describes the basic steps in the examination of the eye. The reader is then taken through a range of common primary eye care problems, with the emphasis on their management by the non-specialist. The discussion of surgical procedures is kept to a minimum, with most space being given to non-surgical ophthalmic problems. These are described in nine chapters and include 'The ageing eye,' 'The child's eye,' 'The systemic disease and the eye,' and 'Neurophthalmology.' The text is not referenced; however, suggestions for further reading are given at the end of most sections.

The black-and-white illustrations are clear and well chosen and the clinical figures interspersed with amusing cartoons. The fundus photographs, however, suffer as a result of poor reproduction and the lack of colour. One serious omission is the absence of discussion of the afferent pupillary defect, a sign which is so important for the medical student and the non-specialist to be able to recognise. In conclusion, this book should be read by every general practitioner, and with the increasing attention being given to ophthalmology in the medical school curriculum it should be read by every medical student.

ZDENEK J GREGOR

Notes

Study grants

Glaucoma Group Travel Fellowship. Sponsored by Merck Sharp and Dohme, this will assist a visit to a hospital or research centre during the academic year starting 1 October 1986. The award will be equivalent to £1500. The purpose of the award is to enable the successful applicant to gain experience and knowledge in pursuit of a specific project related to glaucoma.

Glaucoma Group Research Grant. Sponsored by International Glaucoma Association, this will be available for a clinically orientated research project related to glaucoma for 1986. The award will be equivalent to £2500. It may be used towards salary or project expenses or for buying equipment.

Both these awards are available to medical graduates and non-medical scientists resident in the United Kingdom or Eire. They may be held concurrently with other awards. A curriculum vitae should be sent with information on the applicant's research project and details of proposed visit (preferably with confirmation from the centre(s) visited) to: Dr S Nagasubramanian, Glaucoma Group Secretary, Glaucoma Unit, Moorfields Eye Hospital, High Holborn, London WC1V 7AN. The closing date for applications is 14 June 1986. The successful candidate will be informed by August 1986.

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Mr N Harold L Ridley has been elected a Fellow of the Royal Society. Mr Ridley was formerly honorary consultant surgeon at Moorfields Eye Hospital and at St Thomas's Hospital, London. He is distinguished in particular for his innovative and highly successful treatment of blindness caused by cataract using inert acrylic implants to replace the lens of the human eye.

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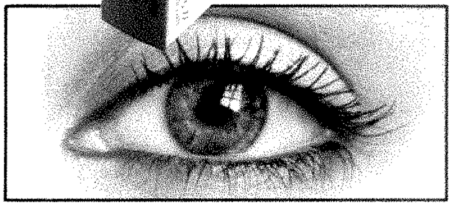

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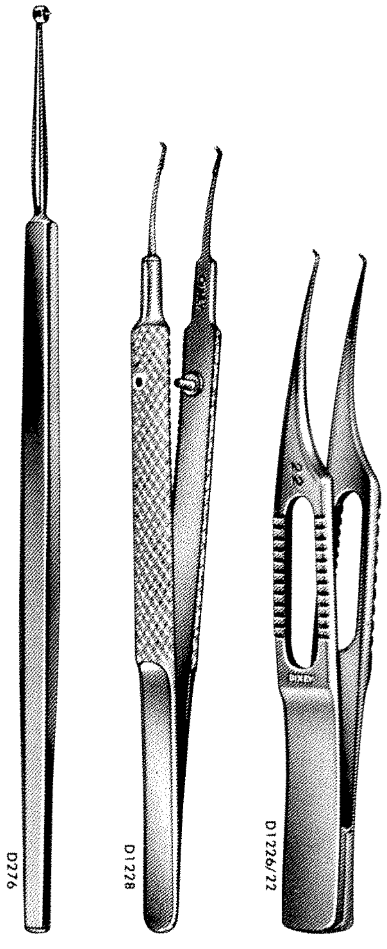

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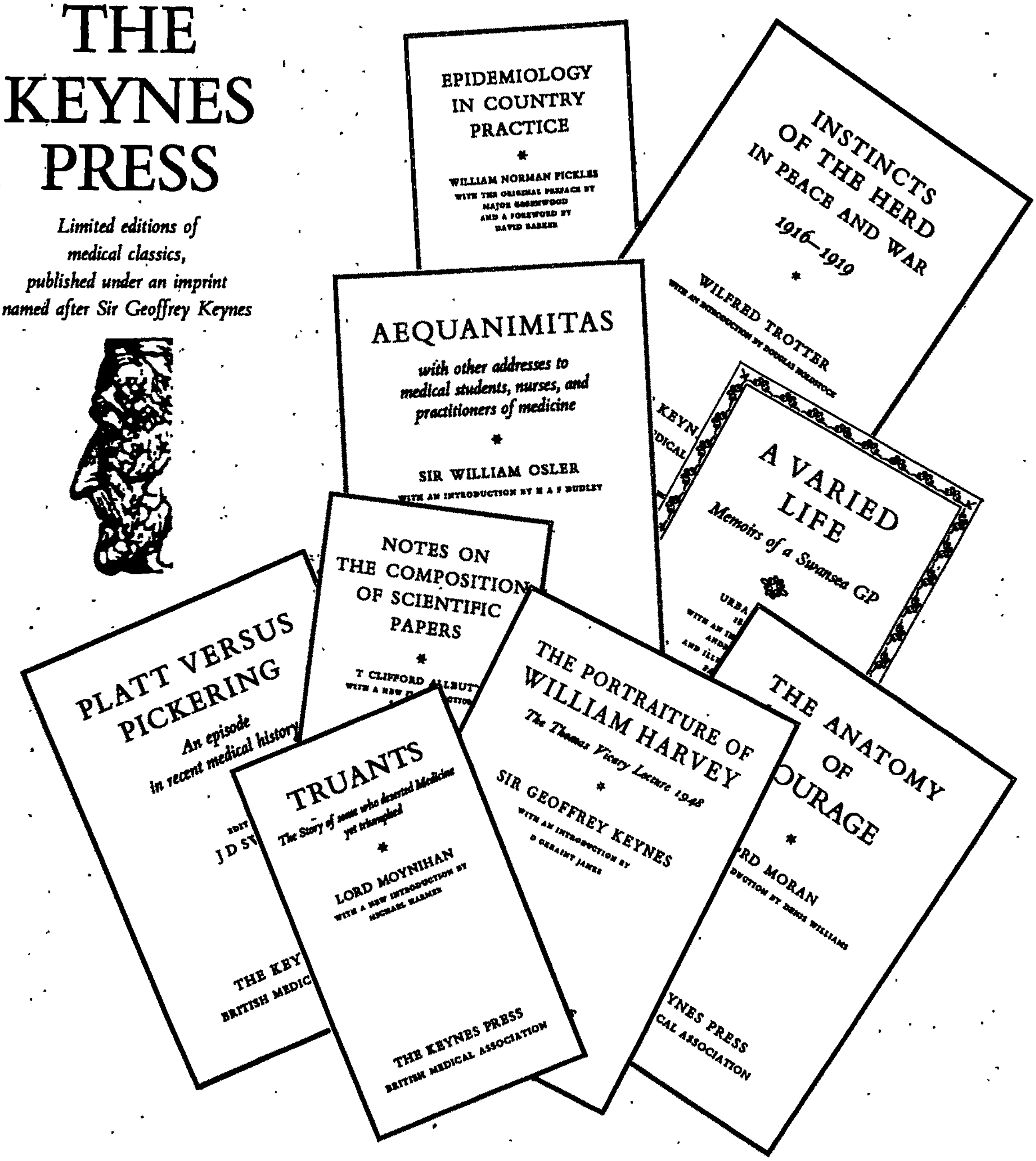
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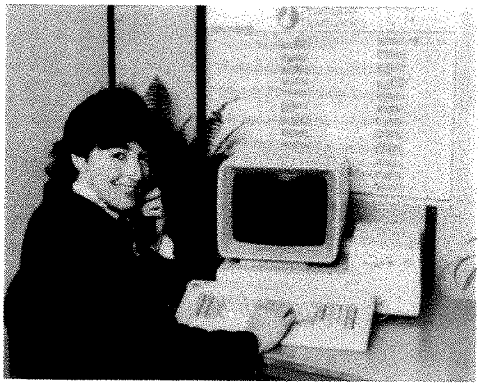

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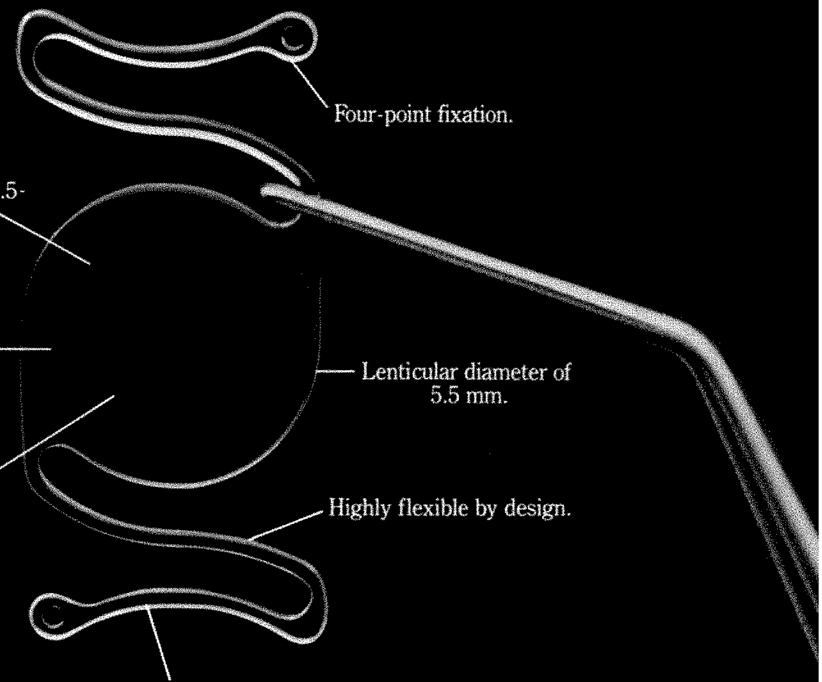

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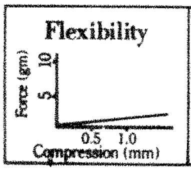

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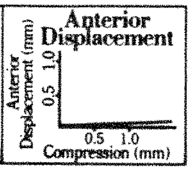

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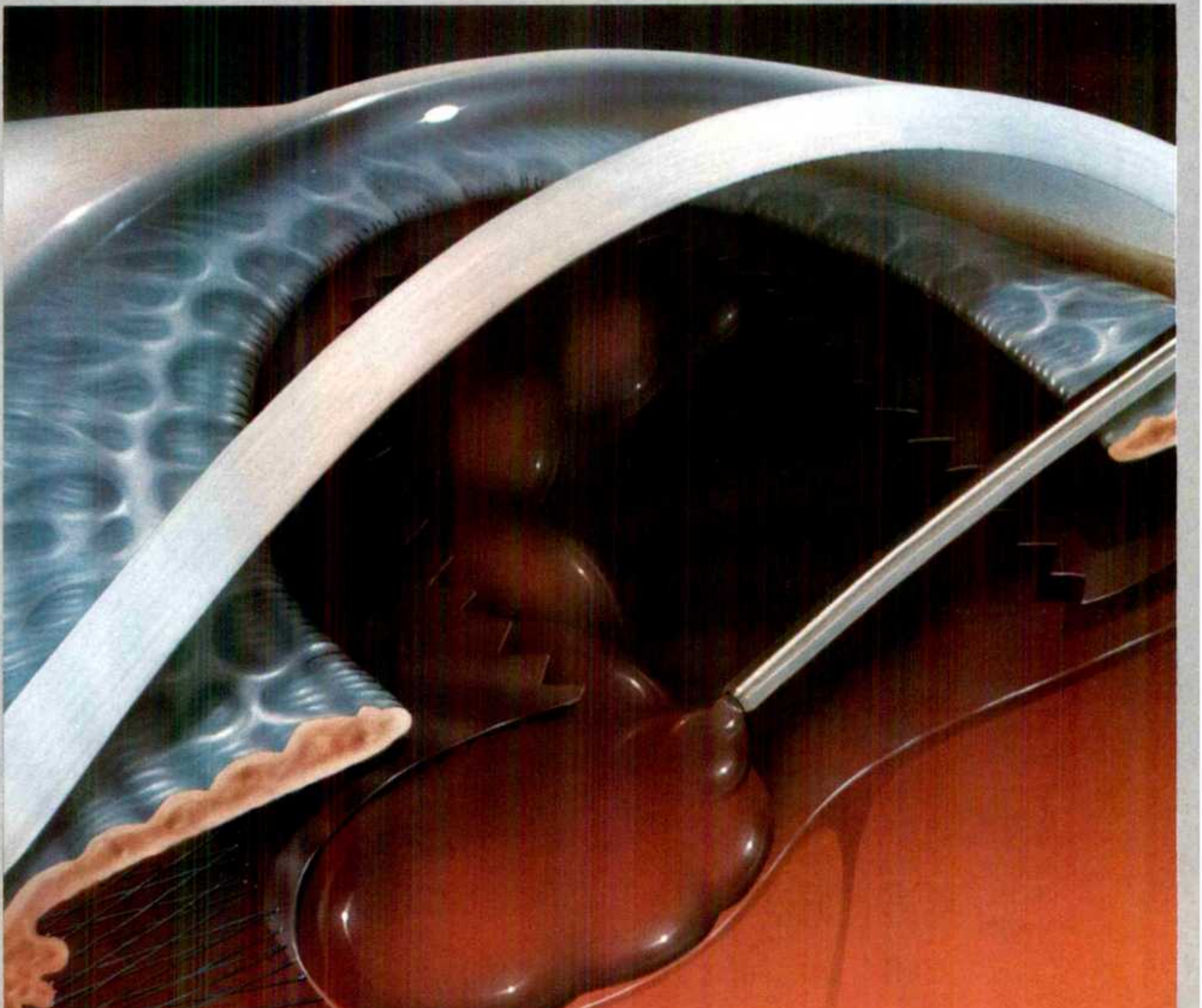

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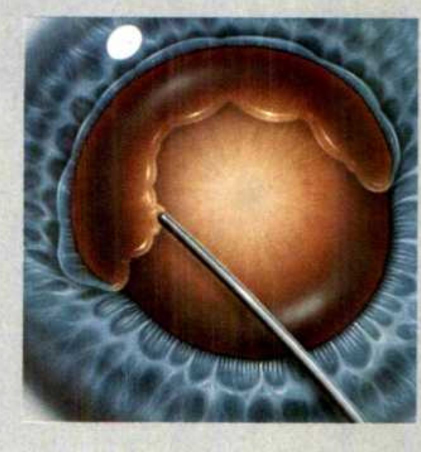

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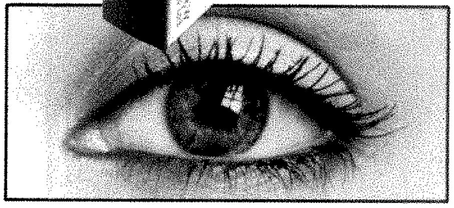

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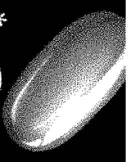

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Experimental posterior perforating ocular injury: a controlled study of the gross effects of localised gamma irradiation

U CHAKRAVARTHY, C J F MAGUIRE, AND D B ARCHER

From the Department of Ophthalmology, Royal Victoria Hospital, Belfast, Northern Ireland

SUMMARY A pilot study on the effect of localised irradiation applied to the site of a standard perforating injury in the rabbit eye, showed that gamma rays limited the formation of post-traumatic vitreoretinal membranes. A controlled study was therefore undertaken to confirm this observation. Twenty-four pairs of rabbits underwent a standard perforating injury in the right eye. One rabbit of each pair received a radioactive ophthalmic ^{60}Cobalt applicator and the other a dummy applicator. Nineteen of 24 non-irradiated eyes developed vitreoretinal membranes, with associated traction retinal detachment. Only four of 24 irradiated eyes developed traction retinal detachment.

Post-traumatic retinal dysfunction is a major cause of partial or complete visual loss following perforating injuries of the eye.[1,2] In such eyes the proliferation of cells at the site of injury gives rise to vitreoretinal membranes, a condition known as proliferative vitreoretinopathy (PVR).[3-5] The subsequent contraction of these membranes may detach the retina from the underlying pigment epithelium and choroid, resulting in damage to retinal structure and impairment of retinal function.

Histological studies of post-traumatic vitreoretinal membranes have shown that the majority of the cells are fibroblasts, retinal pigment epithelial cells, glial cells, and macrophages embedded in a collagen and fibrin matrix.[6-10] Some cells with the properties of fibroblasts are seen in ultrastructural studies to contain contractile proteins and to have certain characteristics of smooth muscle cells.[11,12] Such cells are termed myofibroblasts, and their contractile properties are probably responsible for active contraction of vitreoretinal membranes.[10] The matrix on which the myofibroblasts exert traction is provided by the vitreous framework or collagen elaborated by the fibroblasts themselves.[13]

The management of PVR is principally surgical, involving vitrectomy and removal of membranes to permit repositioning of the retina.[14] Although anatomical success may be achieved, visual results may be disappointing.[15] Furthermore the manipulation and cutting of vitreous bands during vitrectomy may promote the formation of new membranes.[16] Attempts have been made to limit membrane formation by the use of corticosteroids.[17] These drugs not only limit the invasion and lysis of the vitreous collagen by inflammatory cells but also have an inhibitory effect on the growth of fibroblasts. However, intraocular structures are largely inaccessible to drugs administered on conventional lines, and, despite intravitreal injection of large doses of corticosteroids, the drug disappears too rapidly to provide sustained inhibition.[17]

Antimitotic agents, which are inhibitors of cellular proliferation, particularly 5 fluorouracil, have been used recently with some success in patients with proliferative vitreoretinopathy.[18] This drug is toxic to the retina and capable of abolishing the electroretinogram at doses very close to the therapeutic range.[19] Because of increased clearance of fluorouracil from eyes subjected to vitrectomy, repeated administration of the drug is necessary to achieve a therapeutic effect. This can result in peak intraocular levels of the drug after each injection, and its intraocular use in conjunction with gas tamponade may result in its concentration at toxic levels on the retinal surface.[20]

β-aminopropionitrile[21] and penicillamine[22] have been tried in experimental animal studies. Both

Correspondence to Miss U Chakravarthy, FRCS, Department of Ophthalmology, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, Northern Ireland.

drugs reduce the formation of new collagen by inhibiting enzymes that are responsible for the cross linking between collagen molecules. The fibroblasts are therefore deprived of a scaffolding on which to grow and exert their contractile force.

Haematoporphyrin photoradiation therapy has been tested in the animal model.[23] Haematoporphyrin derivative binds wells to the cell membrane of dividing cells and, when followed by photoradiation, results in destruction of the cell.

Ionising irradiation offers an alternative approach in the management of proliferative vitreoretinopathy. It had long been known to inhibit the growth and division of cells, and this property of gamma rays has been studied extensively in tissue culture.[24,25] Belkin *et al.* used single-dose, whole-eyeball, gamma irradiation with some success to inhibit the formation of experimental post-traumatic intraocular membranes.[26] Such vitreoretinal membranes can be created successfully and reproducibly in the experimental animal model,[27] and the cellular proliferation and membrane formation is most pronounced at the site of perforation.[27,28] We therefore considered the local application of gamma rays to the site of injury as a logical method of preventing the formation of vitreoretinal membranes.

Radioactive ^{60}cobalt applicators originally devised by Stallard[29] working in conjunction with Innes[30] have been used extensively in the treatment of neoplasms of the eye. The ophthalmic ^{60}cobalt applicator was therefore chosen as a convenient source of ionising rays to provide continuous irradiation at the site of injury. The CKA 1 applicator (Amersham International PLC) has an external diameter of 7 mm and a distribution of radioactive ^{60}cobalt (internal diameter 5 mm) within a platinum casing (activity 26 MBq). When it is applied to the sclera, the tissue-absorbed dose in the central axis of the plaque, calculated by established dosimetry curves,[31] at a depth of 1 mm, is 50 Gy/24 hours, and at a depth of 4 mm is 11 Gy in 24 hours (Figs. 1A and 1B). It was considered advantageous to have such a depth-dose relationship, since the proliferating membrane has its origins at the wound. This site would therefore receive maximum irradiation, while the level of irradiation received by tissues at a greater distance from the plaque and remote to the central axis would be greatly reduced.

Radiation retinopathy following application of a ^{60}cobalt plaque to neoplasms of the eye has been reported with doses in excess of 50 Gy to the tumour apex when the height of the tumour was 5–10 mm.[32] This resulted in doses in excess of 450 Gy to the retina and choroid, which are anatomically closer to the plaque. With localised doses of less than 200 Gy to the retina and choroid, radiation retinopathy does not occur, though scarring results with nerve fibre loss. However, even this dose may be toxic if the plaque is applied over the central retina or the major blood vessels.[33] We chose to apply the radioactive ^{60}cobalt plaque to the peripheral sclera for 48 hours, at which time the sclera received a dose of 100 Gy and the retina and choroid received a dose of approximately 80 Gy. This dose was less than the minimum

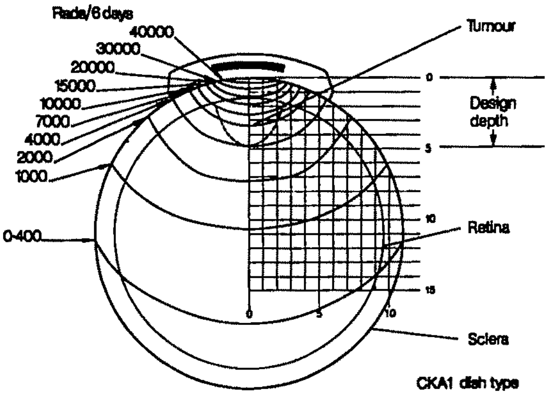

Fig. 1A *Isodose curves for CKA 1 plaque (reproduced by courtesy of Amersham International PLC).*

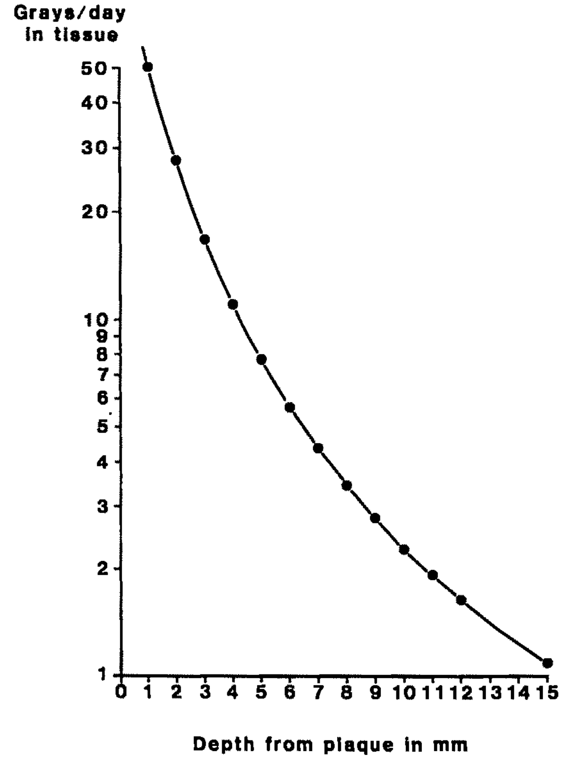

Fig. 1B *Central axis dose rate for CKA 1 plaque.*

Table 1 *Details of post-mortem appearance of the four non-irradiated and four irradiated eyes which constituted the pilot study. Two animals, one irradiated and the other a control, developed an infective endophthalmitis and were excluded from the pilot study*

Time of death after injury	*Non-irradiated eyes*		*Irradiated eyes*	
	Serial number	*Post-mortem appearance*	*Serial number*	*Post-mortem appearance*
7 Days	10	The blood clot was loculated in mid-vitreous. Condensed vitreous and fibrin bands extended from the site of perforation to retina opposite the wound	5	The blood clot was loculated in mid-vitreous and fibrin bands extended from the site of perforation into the vitreal blood clot and to retina diametrically opposite the wound
14 Days	7	A greyish membrane stretched from the wound into the vitreous, and along the surface of the retina, adjacent to the site of perforation	1	The wound was sealed on the retinal aspect by greyish fibrous tissue. Tenuous fibrinous bands extended from the wound into the vitreous
21 Days	2	A vitreoretinal membrane was present at the site of perforation, attaching distally to the medullary rays, ciliary body, nasal retina, and lens. A traction retinal detachment involved the medullary rays and nasal retina	3	The site of injury was represented by a pigmented chorioretinal scar. The vitreous was clear apart from blood remnants
42 Days	6	There was extensive membrane formation with a total retinal detachment	4	A membranous stalk stretched from the site of perforation into the vitreous with no distal attachment. At the base of the stalk a chorioretinal scar with surrounding pigmentation indicated the site of injury

tumoricidal doses used in the past and half the minimum reported dose likely to cause radiation retinopathy.

We performed a pilot study on 10 rabbit eyes that were subjected to a standard perforating injury based on the Cleary and Ryan animal model.[34] Five of these rabbits acted as controls, and the injured eye of the remaining five rabbits was irradiated with the 5 mm CKA 1 ophthalmic ^{60}cobalt applicator (external diameter of 7 mm) for 48 hours after injury. The rabbits were killed sequentially for a period of up to six weeks and the details of the post-mortem findings are given in Table 1. Non-irradiated eyes developed extensive vitreoretinal membranes, with associated traction retinal detachement. Irradiated eyes by contrast developed focal scars at the site of injury, and, if a membrane was present, it was attenuated without distal attachment to other intraocular structures. A controlled study was therefore carried out on 48 pigmented rabbits in order to confirm this finding statistically.

Materials and methods

Pigmented rabbits, weight 2 kg, of either sex were used. The animals were randomly divided into two groups of 24 each, one of which was assigned to receive the radioactive ^{60}cobalt plaque and the other a dummy plaque, the key to the code being held by the animal technician. The dummy plaque was identical in appearance with the radioactive applicator, so that observer bias was eliminated, and both radiated and control rabbits underwent standardised surgical proceedures. The rabbits were anaesthetised in pairs with pentobarbitone 60 mg/kg body weight, and the anaesthesia supplemented with 1% retrobulbar lignocaine. The right eye of each animal was subjected to a standard perforating injury,[34] which consisted of a conjunctival peritomy that was performed in the inferior temporal quadrant, and the globe was then perforated by a full-thickness 5 mm circumferential incision 4 mm behind the limbus with a Bard-Parker scalpel blade. 0·2 ml of vitreous was aspirated through the wound with a 20 gauge needle and replaced with the same quantity of autologous blood drawn from the rabbit's ear vein. The scleral wound was approximated with two 5–0 Ethibond sutures. On the basis of the preselected code either a radioactive or a dummy plaque was sutured over the sclera to cover the site of perforation (Fig. 2). The conjunctiva was drawn up over the plaque and secured to the limbus by a single stitch.

The injured eyes were examined daily for the first week and weekly thereafter. The extent and density of vitreous haemorrhage and haze were assessed and scored on days 3 and 5; and later, when present vitreoretinal membranes were graded on their extent and traction effects, on weeks, 2, 4, 6, 8, and 12

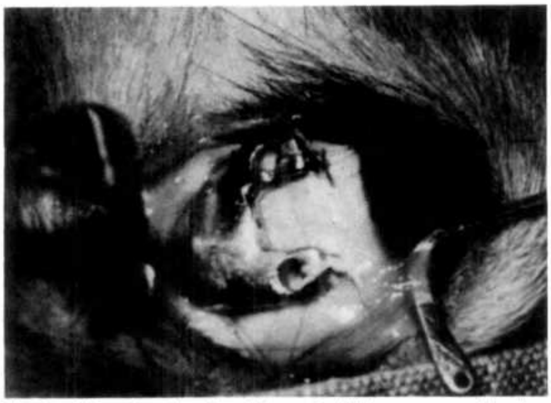

Fig. 2 *Site of perforating injury of rabbit eye covered by the ophthalmic ^{60}cobalt applicator.*

Table 2 *Details of ophthalmoscopic appearance as graded and scored on day 3 and day 5 and weeks 2-12: key to codes used for ophthalmoscopic detail*

Grade	
Days 3 and 5	
1	Retina clearly visible
2	Retina visible through haze
3	Retina obscured 1 quadrant
4	Retina obscured >1 quadrant
5	Retina obscured entirely
Weeks 2–12	
1	Scar only
2	Fibrinous strands
3	Membrane with no distal attachments
4	Membrane attached to intraocular structures with or without early detachment
5	Membrane causing extensive retinal detachment

(Table 2). Four eyes suffered an accidental traumatic lens injury at the time of injection of blood into the vitreous, and subsequently developed lens opacities. One rabbit was found to have a second full-thickness perforation of the globe just inferior to the medullary rays in the temporal quadrant caused by the injecting needle. All these animals were included in the study. The animals were killed sequentially at 1, 2, 3, 4, 6, and 12 weeks. Eight injured eyes were harvested at each time interval, four of which had been irradiated. The eyes were fixed in 10% formalin for 24 hours, after which the anterior segment was removed and the posterior half of the globe photographed.

The size and extent of the vitreal blood clot, the length of the proliferative tissue, and its traction effects and the presence of a retinal detachment were graded and scored (Table 3). Scleral wound healing was assessed on the ability of the granulation tissue to withstand the stress of sectioning the eyeball. If the lips of the wound stayed together, it was considered that healing was established. If the granulation tissue bridging the wound disintegrated on sectioning the eyeball, the wound was considered as poorly healed. The wound and proliferative tissue were processed for light microscopy and 7 μm sections were stained with haematoxylin and eosin.

Results

OPHTHALMOSCOPIC APPEARANCE

The results are summarised in Table 4. In both non-irradiated and irradiated eyes immediately after injury and injection of blood the vitreous haemorrhage obscured all retinal details.

Non-irradiated eyes. At day 3 vitreous haze was quite marked and prevented examination of the retina. By day 5 clearing of peripheral vitreous opacities had begun, and the injured retina was visible on ophthalmoscopy. Fibrinous strands and condensed vitreal fibrils extended from the site of injury into the mid-vitreal blood clot and towards the medullary rays of the retina. During week 2 greyish membranes appeared initially at the site of perforation but later extended along the fibrinous tracks into the vitreous. The membranes typically attached themselves to the medullary rays and retina directly opposite the wound, causing retinal folding at these sites. They also became attached to the ciliary body, retina adjacent to the wound, and the posterior surface of the lens. At week 3 localised traction retinal detachments were established at some points where the proliferative membrane was adherent to

Table 3 *Codes used to score appearance of the vitreal blood clot, length of vitreoretinal membrane, and the traction effects*

	Grade
Blood clot	
None	1
Clot <2 mm diameter	2
Clot 2–5 mm diameter	3
Clot 5–10 mm diameter	4
Clot filling vitreous chamber	5
Length of stalk or proliferating membrane	
Stalk absent	1
Stalk <2 mm long	2
Stalk 2–5 mm long	3
Stalk 5–10 mm long	4
Stalk filling vitreous chamber	5
Traction effects and distal attachments of stalk	
Absent stalk with no traction	1
Stalk with no distal attachments and no traction	2
Stalk attached to one intraocular structure with or without local retinal detachment	3
Stalk attached to more than one intraocular structure with or without local retinal detachment	4
Extensive stalk with total retinal detachment	5

Table 4 *The ophthalmoscopic scores of non-irradiated and irradiated eyes arranged by week of animal's death. At later weeks irradiated eyes had lower scores when compared with non-irradiated eyes.*

Non-irradiated							*Irradiated*						
Serial Number	*Ophthalmoscopic appearance*						*Serial Number*	*Ophthalmoscopic appearance*					
	Day 3	*Day 5*	*Week 2*	*Week 4*	*Week 6*	*Week 12*		*Day 3*	*Day 5*	*Week 2*	*Week 4*	*Week 6*	*Week 12*
2	3	2					7	3	3				
3	4	3					22	4	3				
12	3	3					4	2	1				
48	3	2					42	4	4				
10	4	4	4				45	4	3	3			
23	4	3	5				18	3	2	1			
30	3	4	4				14	3	2	2			
33	5	5	5				29	3	2	2			
8	3	3	4				27	3	3	2			
20	4	5	4				17	3	3	2			
21	3	3	4				9	3	3	1			
41	5	4	2				40	5	4	3			
1	4	4	3	3			35	3	2	1	1		
19	3	3	1	1			26	3	3	3	3		
25	4	5	4	4			16	4	4	3	3		
32	4	4	2	2			43	3	2	1	1		
6	3	3	4	4	4		15	3	2	1	1	1	
13	4	3	3	4	4		44	4	4	2	2	1	
38	3	3	2	3	3		39	3	3	3	4	4	
47	4	3	3	4	4		36	4	3	3	2	2	
5	4	3	3	4	4	5	31	4	4	3	3	2	1
11	4	3	2	2	2	2	46	4	3	4	4	4	4
24	4	3	3	3	3	3	37	4	3	2	2	1	1
28	3	3	3	4	4	4	34	3	3	1	1	1	1

the retina. All four eyes that were observed for 12 weeks had subtotal of total retinal detachments, with extensive intraocular proliferation. Two of the non-irradiated eyes (animals 33 and 20) had an inadvertent lens injury. Both these eyes had a severe postoperative inflammatory reaction, and retinal detachment was present as early as one week.

Irradiated eyes: On day 3 cloudy vitreous obscured the retina as in the control eyes. By day 5 clearing of the peripheral vitreal blood clot had begun, and at week 2 the media were sufficiently clear to permit observation of the injury site by ophthalmoscopy. The injured retina was oedematous, and strands of fibrin, condensed vitreal fibrils, and blood extended from the site of injury into the mid-vitreous. At around 10 days these strands became attenuated in approximately half the eyes, but in others they were replaced by greyish membranes that stretched for short distances into the vitreous from the site of perforation. In most of the latter the distal ends of the membranes appeared to float freely in the vitreous without attachment to other intraocular structures.

Between weeks 3 and 12 vitreous opacities in most irradiated eyes continued to clear with no further membrane formation. Of the 12 irradiated eyes that were followed up for more than four weeks three developed traction retinal detachments due to proliferative vitreoretinopathy. One of the animals (rabbit 16) suffered a lens injury. This eye developed a severe uveitis in the immediate postinjury phase, and by week 2, when the vitreous debris had cleared, a vitreoretinal membrane and traction retinal detachment at sites of adherence of the membrane became obvious. The second of the irradiated eyes that developed PVR (rabbit 46) suffered a double perforating injury. This eye developed a vitreoretinal membrane and traction detachment at the exit wound. The site of the entry wound remained flat. The third of the irradiated eyes that developed retinal detachment (no 39) had no additional injury and yet fared badly. This eye developed a local retinal detachment of the medullary rays.

Statistical analysis was performed by the non-parametric Mann-Whitney U test on ophthalmoscopic scores of non-irradiated and irradiated eyes. The results were insignificant at the 5% level at day 3 and day 5. However, there was a significant difference in scores between the two groups at all the remaining time intervals studied ($p<0{\cdot}05$).

POST-MORTEM APPEARANCE

Non-irradiated eyes

The results are summarised in Table 5.

Week 1. Three of four non-irradiated eyes had

Table 5 *Details of post-mortem appearance of non-irradiated eyes*

Time of death	*Serial number*	*Wound*	*Vitreoretinal membrane*		
			Length in mm	*Distal attachments*	*Traction effects*
1 Week	2	Gaping	<2	None	None
	3	Healed	2–5	MR	RF
	12	Healed	2–5	MR	None
	48	Healed	5–10	PR, CB, Lens	RF
2 Weeks	10	Healed	5–10	MR, CB, PR	STRD
	23	Gaping	>10	PR, OR, Lens	LRD
	30	Healed	>10	MR, OR, CB	TRD
	33*	Healed	>10	MR, CB, Lens	TRD
3 Weeks	8	Healed	2–5	PR	LRD
	20*	Healed	>10	MR, CB	TRD
	21	Healed	2–5	PR	LRD
	41	Healed	2–5	PR	None
4 Weeks	1	Healed	2–5	PR	RF
	19	Healed	2–5	None	None
	25	Healed	>10	MR	LRD
	32	Healed	5–10	MR	LRD
6 Weeks	6	Healed	2–5	PR, CB	LRD
	13	Healed	2–5	MR	RF
	38	Healed	2–5	None	None
	47	Healed	5–10	MR, OR	LRD
12 Weeks	5	Healed	>10	MR, PR, CB	TRD
	11	Healed	>10	MR, PR, CB	STRD
	24	Healed	2–5	PR	LRD
	28	Healed	5–10	OR, CB	STRD

Ciliary body CB, localised retinal detachment LRD, medullary rays MR, opposite retina OR, peripheral retina PR, retinal folds RF, subtotal retinal detachment STRD, total retinal detachment TRD.
*Animals 33 and 20 suffered an accidental lens injury.

healed scleral wounds. In one eye the granulation tissue bridging the wound disintegrated on sectioning the eyeball. In all eyes blood clot was present on the inner aspect of the wound and extended into the vitreous. In two eyes fibrinous bands and condensed vitreal fibrils stretched from the site of perforation to the medullary rays and retina directly opposite the wound. In two other eyes a definite membrane was present, and this extended from the wound into the vitreous blood clot. In both these eyes the membrane had distal attachments to the medullary rays, ciliary body, and opposite retina. Traction at these sites was evident as retinal folding or wrinkling.

Week 2. Three of four non-irradiated eyes had healed scleral wounds. In all eyes the blood clot was replaced by fibrous vitreoretinal membranes (Fig. 3), which were thicker and more extensive than those present at week 1. One eye had extensive exudation into the vitreous and a total retinal detachment. This eye had a lens injury.

Week 3. All eyes had healed scleral wounds. One untreated eye had membrane formation with no traction on the retina. Two eyes had membranes exerting localised traction on the retina, and one had extensive proliferative vitreoretinopathy and total retinal detachment. This eye had suffered a lens injury.

Week 4. Scleral wound healing was well established in all four eyes. The fibrous membrane, which was present in all four eyes harvested at this time interval, extended into the vitreous from the site of injury and over the retinal surface. Three of the eyes had localised retinal detachments and one had a total retinal detachment. Pigmentary changes were present adjacent to the site of injury.

Week 6. Three eyes had a fibrous membrane adherent to peripheral retina causing a traction retinal detachment. One eye had a short membrane whose distal end did not become attached to other structures, the retina staying flat.

Week 12. All four eyes had extensive intraocular membrane formation (Fig. 4). Three of these had total retinal detachment and one had a localised retinal detachment. The blood clot had undergone further lysis and shrinkage.

Irradiated eyes

Results are summarised in Table 6.

Week 1. Three of four irradiated eyes had poorly healed scleral wounds. Blood clot was present in the vitreous adjacent to the wound. Fibrinous bands and

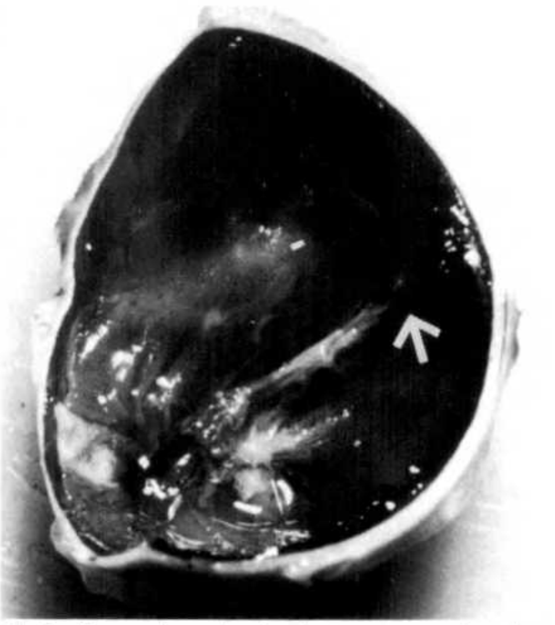

Fig. 3 *Two-week non-irradiated post-mortem sectioned eyeball (rabbit 10), showing site of perforation (double black arrows), with proliferation spreading over retinal surface. Elevated traction band* (p) *extending between site of perforation and medullary rays (white arrow).*

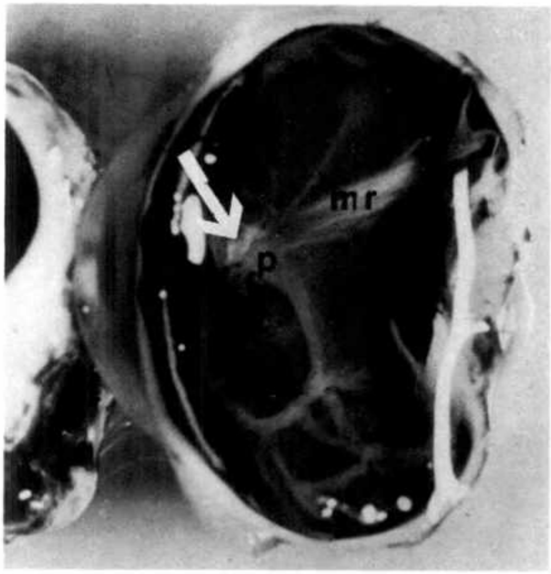

Fig. 4 *Post-mortem non-irradiated 12-week sectioned globe (rabbit 5), showing site of perforation (white arrow) with proliferation extending over surrounding retina. Total retinal detachment, with traction tear of retina adjacent to the site of perforation. mr=medullary rays.*

Table 6 *Details of post-mortem appearance of irradiated eyes*

Time of death	*Serial number*	*Wound*	*Vitreoretinal membrane*		
			Length in mm	*Distal attachments*	*Traction effects*
1 Week	7*	Gaping	2–5	CB, Lens	LRD
	22	Gaping	<2	None	None
	4	Gaping	<2	None	None
	42	Gaping	2–5	None	None
2 Weeks	45	Gaping	2–5	None	None
	18	Gaping	0	None	None
	14	Healed	0	None	None
	29	Gaping	<2	None	None
3 Weeks	27	Healed	<2	None	None
	17	Healed	<2	None	None
	9	Healed	0	None	None
	40	Healed	2–5	PR	None
4 Weeks	35	Healed	0	None	None
	26	Healed	2–5	CB	None
	16*	Healed	>10	MR, OR, CB	TRD
	43	Healed	0	None	None
6 Weeks	15	Healed	<2	None	None
	44	Healed	0	None	None
	39	Healed	>10	MR, Lens	STRD
	36	Healed	<2	None	None
12 Weeks	31	Healed	0	None	None
	46†	Healed	5–10	CB, OR, Lens	LRD
	37	Healed	<2	None	None
	34	Healed	<2	None	None

Ciliary body CB, localised retinal detachment LRD, medullary MR, opposite retina OR, peripheral retina PR, retinal folds RF, subtotal retinal detachment STRD, total retinal detachment TRD.
*Animals 7 and 16 suffered a lens injury.
†Animal 47 suffered a double perforation.

condensed vitreal fibrils extended from the site of perforation to retina diametrically opposite the wound. Only one of the four eyes had membrane formation, associated with a peripheral retinal detachment. This animal suffered a lens injury, and an inflammatory exudate filled the eye (rabbit 7).

Week 2. Half the irradiated eyes had healed scleral wounds. The blood clot exhibited signs of lysis and shrinkage. Attenuated membranes were present in two of the irradiated eyes, with the distal end of the stalk lying free in mid-vitreous. Two eyes had no membrane formation, and all four eyes had flat retinae.

Week 3. All four irradiated eyes had healed scleral wounds. The retina overlying the site of perforation had been replaced by flat scar tissue in one eye. Two had vitreal membranes with no distal attachments, and one eye had a fibrous band which stretched from the wound to the opposite retina. In this eye traction was not evident and the retina remained flat.

Week 4. Two of four irradiated eye had short vitreoretinal membranes, one of which caused a traction retinal detachment. This eye (rabbit 16) had suffered a lens injury. Two others had flat chorioretinal scars with pigmentary changes in the surrounding peripheral retina.

Week 6. One eye had a healed retinal wound with extensive pigmentary changes in the inferior temporal quadrant of the retina. Two eyes had membranes exerting no traction; one had a proliferation attached to the medullary rays, causing a localised retinal elevation at that site (rabbit 39).

Week 12. In all eyes scleral wound healing was complete and the blood clot had undergone further lysis and disintegration. Pigmentary disturbance was present in the injured quadrant in all specimens. Two eyes showed retinal scarring and no membrane formation (Fig. 5) one had an attenuated membrane, while another which had suffered double perforating injury had a vitreoretinal membrane (rabbit 46). The membrane extended from the exit wound which lay in the inferior nasal quadrant to the medullary rays, where it caused a local retinal detachment.

Statistical analysis was performed on the post-mortem scores for each measurement at each time interval studied. There was no significant difference between the size of blood clot in non-irradiated and irradiated eyes at any of the time intervals studied. However, scores for the length of the proliferative membrane and its traction effects showed significant differences between the two groups for all time intervals between weeks 2 and 12 ($p<0{\cdot}05$), and at

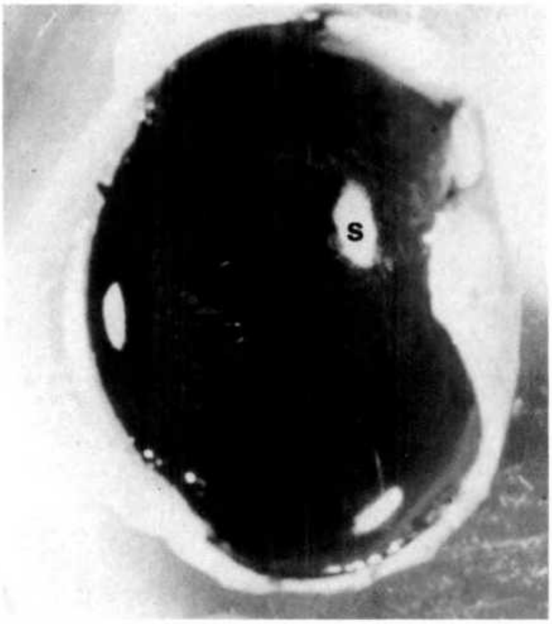

Fig. 5 *Irradiated 12-week post-mortem sectioned globe (rabbit 31), showing a retinal scar* (S) *with surrounding pigmentary changes.*

weeks 6 and 12 the difference in scores was considered highly significant ($p<0{\cdot}01$). At week 1 the difference in scores was not considered significant for the length of the proliferation or its traction effects ($p>0{\cdot}05$).

LIGHT MICROSCOPIC APPEARANCE

Histological examination of the wound and proliferative tissue showed that non-irradiated eyes had abundant collagen deposition and highly cellular membranes. In irradiated eyes the newly formed collagen in the region of the wound was sparse, and the chorioretinal scars were flat and atrophic. Though vitreoretinal membranes were not a constant feature of irradiated eyes, the membranes which developed were attenuated and poorly cellular with a sparse collagen matrix. An account of the light microscopic features of the wound and attached proliferation in non-irradiated and irradiated eyes will be published in conjunction with the results of a parallel autoradiographic study.

Discussion

Post-traumatic vitreoretinal membranes develop at the site of trauma and extend to involve other intraocular structures. In this study we have shown that local application of irradiation to the site of injury results in limitation of membrane formation and therefore reduction in the incidence of retinal detachment. Most non-irradiated eyes developed PVR and had extensive membranes which frequently attached to other intraocular structures, causing retinal detachment (19 of 24 eyes). Approximately half the irradiated eyes had no membrane formation and developed flat atrophic chorioretinal scars. Some of the irradiated eyes did develop vitreoretinal membranes, but these were attenuated and their distal ends had fewer attachments to other intraocular structures. Consequently retinal detachment occurred infrequently in irradiated eyes (4 of 24 eyes).

Non-irradiated eyes had healed scleral wounds by week 2. In irradiated eyes scleral wound healing was delayed when compared with the non-irradiated group. Wound healing, however, was complete in irradiated eyes at 4 weeks. Both non-irradiated and irradiated eyes showed pigmentary changes in the area immediately adjacent to the wound. In irradiated eyes, however, the pigmentary changes were more marked and extended to involve an entire quadrant of the retina round the site of injury. One animal in our study suffered a double perforation resembling the Topping and Machemer animal model of traction membranes.[28] They showed that a band of proliferative tissue formed between entry and exit wounds. In rabbit 46 a traction band did not develop at the site of the standard injury which was irradiated. However, epiretinal and vitreal membranes developed at the site of the exit wound, causing a local retinal detachment. Those eyes that suffered an accidental lens injury fared worse than the others in either group. Such an injury provoked an acute inflammatory reaction and appeared to promote cellular proliferation and earlier membrane formation remote from the maximum activity of the plaque.

In conclusion, gamma irradiation was found to be effective in arresting the development of vitreoretinal membranes following a standard perforating injury of the eye, when applied directly to the site of perforation. Wound healing was delayed but not prevented. Electron microscopy of the ocular tissues at the irradiated site and remote from the site of irradiation is being undertaken. Further studies on the optimum time of application of the plaque and the minimum effective dose of radiation are in progress.

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Pseudoepiphora from cerebrospinal fluid leak: case report

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SUMMARY A 4-year-old tearing child with obstruction of the nasolacrimal duct was treated with dacryocystorhinostomy three years after naso-orbital injury. However, what appeared to be tearing peristed, and meningitis developed. Coronal CT scans demonstrated traumatic encephalocele of the posterior superior orbital roof. A chronic orbital cerebrospinal fluid (CSF) leak was diagnosed. To our knowledge no case of chronic CSF leak has been reported that simulated tearing in an otherwise asymptomatic child. In the tearing patient who has a naso-orbital fracture the possibility of chronic CSF leak should be considered.

Lacrimal outflow obstruction is a well recognised complication of midfacial fractures involving the maxilla, the lacrimal bones, or the ethmoids.[1-4] Common manifestations of obstruction to the lacrimal outflow system include epiphora, dacryocystitis, or mucocele.

A case of epiphora thought to be secondary to nasolacrimal duct obstruction following midfacial trauma is herein described. A 4-year-old child seen two years after naso-orbital injury had traumatic lacrimal duct obstruction and underwent uncomplicated dacryocystorhinostomy (DCR).

The aetiology of tearing in this child was chronic post-traumatic cerebrospinal fluid (CSF) leakage that occurred simultaneously with lacrimal duct obstruction. Despite a successful, DCR, chronic copious CSF leakage simulating tearing continued. To our knowledge this is the first reported case of pseudoepiphora caused by chronic CSF leakage in an otherwise asymptomatic child.

After midfacial fracture chronic CSF leak should be considered in the differential diagnosis of tearing, and the appropriate laboratory and radiographic tests should be performed.

Case report

A 4-year-old boy was seen with epiphora of the right eye of two years' duration. A motor-car accident two years previously resulted in hospital admission, where lethargy progressing to coma and blood in the middle ear led to the diagnosis of basilar skull fracture. Computerised axial tomography (CT) was done three times while he was in hospital and the scans were reported as normal.

Immediately following hospital discharge persistent right-sided tearing was noted. There was no irrigation or pain, and tearing was not related to eating or salivation. Ocular examination showed visual acuities of 20/30 in both eyes. Right inferior oblique overaction was noted with a V-pattern exotropia. Palpation of the orbit revealed no anterior defects and a normally positioned, non-pulsatile globe with no rim defects.

Lacrimal examination with a Jones primary dye test showed no passage of dye after 40 minutes. Traumatic lacrimal drainage obstruction was inferred.

An examination under anaesthesia revealed an obstructed nasolacrimal duct. No fluid could be irrigated through either the upper or lower canaliculus into the nose. Probing revealed a tight internal common punctum and an obstructed nasolacrimal duct.

A dacryocystorhinostomy with canalicular intubation with silicone tubing was performed. The bone was thickened, presumably from past naso-orbital fracture. The patient received 500 mg of intravenous cephazolin (Kefzol) and oral cephalosporins were continued for seven days.

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On the fifth postoperative day mild erythema of the scar site was noted. Tearing had not ceased.

One week after operation the patient developed fever with headache and vomiting. He was admitted to a community hospital with a presumptive diagnosis of periorbital cellulitis and begun on intravenous cephazolin. Two days later he complained of neck pain. A lumbar puncture was done which showed cloudy CSF, raising the possibility of bacterial meningitis. An additional antibiotic was instituted. An axial CT scan was performed which showed air and soft tissue swelling of the right orbit consistent with the operative appearances as well as an opacity of the right ethmoids consistent with the postoperative haemorrhage he had had.

In the ensuing two weeks the patient developed recurrent spiking fevers accompanied by meningeal signs. Intravenous antibiotics were altered to methicillin and chloramphenicol, and he remained afebrile until three weeks after operation, at which time another temperature spike to 101 degrees was noted. The patient was transferred to Tucson Medical Center for further evaluation.

On admission, the temperature was 38·3°C and the vital signs were otherwise normal. No periorbital cellulitis was noted. The dacryocystorhinostomy scar was healing well. The silicone stent was in place. Tearing was persistent and the results of the eye examination were otherwise normal. The medical examination, including a neurological examination, gave results within normal limits. All laboratory tests including examination of the CSF gave normal results.

On the second day in hospital an ophthalmic plastic surgery opinion was sought. The child continued to 'tear' profusely in the right eye. A Jones primary dye test showed dye in the oropharynx at 2 minutes. It was concluded that the dacryocystorhinostomy surgery had been successful and that causes of pseudoepiphora should be sought to explain the 'tearing'.

Our examination included a Dextrostix test of the tear fluid. The sugar content of the tear fluid was observed. The Dextrostix test of the right eye showed a glucose level of 100 to 180 mg/dl (5·6–10·0 mmol/l). The glucose level from the left eye was less than 100 mg/dl (5·6 mmol/l). A specimen of the patient's tears was collected and sent for laboratory analysis. A discrepancy of 2 to 1 in the glucose concentration existed in the right and left eyes. The data strongly suggested CSF leakage into the orbit. A CT scan was performed (Figs. 1 and 2). A gas lucency in the region of the right orbit with thickening of the right medial rectus and opacification of the right ethmoid was observed. Anteriorly the DCR ostium was visible along with thickening of the nasal mucosa (Fig. 1). A bony defect was noted in the posterior orbit that did not communicate with the DCR ostium (Fig. 2).

On the tenth day in hospital a frontal craniotomy was performed. An encephalocele was found into a fracture in the posterior medial orbital roof. It was retracted from the fracture site, and a Silastic implant was placed over the defect. The dural tear was noted and repaired with a free pericranial graft and closed with a single running suture. Postoperatively the patient did well and was discharged six days later. Tearing ceased immediately after surgery. Measured glucose levels in both eyes were the same and less than 100 mg/dl (5·6 mmol/l).

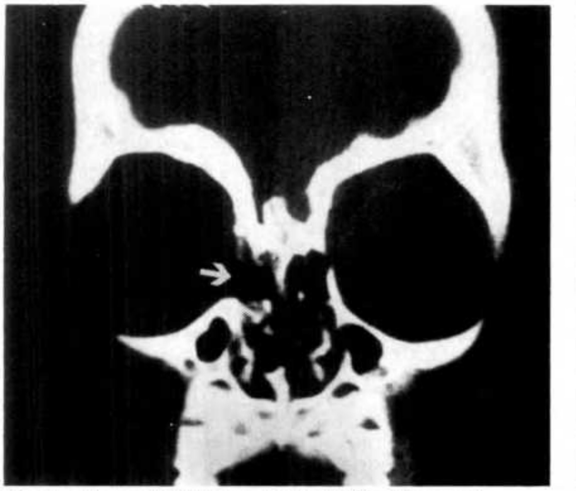

Fig. 1 *Coronal CT demonstrating DCR ostium and thickening of nasal mucosa on the right (arrow).*

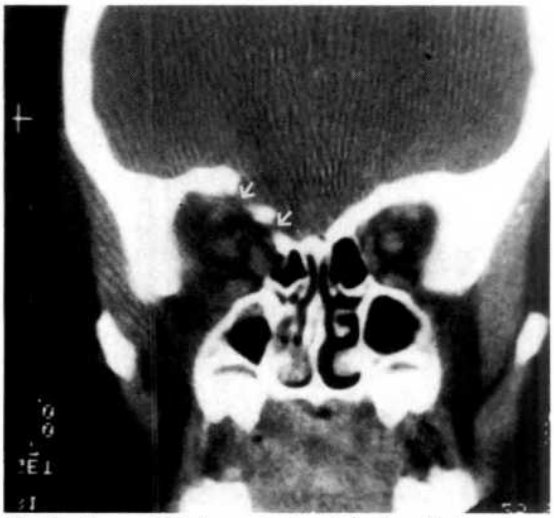

Fig. 2 *Coronal CT demonstrating defect in orbital roof on the right (arrows).*

Discussion

CSF leak has been reported to occur in 6% to 35% of patients with severe non-penetrating intracranial injury.[1,5,9] It occurs in approximately 20% of patients with midfacial fracture or fractures through the paranasal sinuses.[5,9]

CSF leaks are rare in children below the age of 2 because of the flexibility of the cranial base and the relative immaturity of the paranasal sinuses. However, in children older than 2, CSF leakage is by no means uncommon.[10]

Traumatic CSF leaks usually result from tears in the dura at the skull base that allow CSF to escape from the subarachnoid space into the nasopharynx, the paranasal sinuses, or subcutaneously. The floor of the anterior cranial fossa, particularly the cribriform plate area, is thin, and the dura at this site firmly invests the olfactory fissure where the olfactory nerve penetrates the skull. Midfacial trauma may result in penetration of the anterior cranial fossa by ethmoidal roof or wall fragments and dural tear. CSF escapes immediately. If the edges of the dura are in apposition and do not gape, healing is relatively rapid and CSF leak resolves in three to 10 days. Sinus mucosa may bridge a gaping dural defect and cause leakage to cease. However, if bony spicules project through the tear, a portion of the brain herniates through the defect. If a large dural defect is present, healing may be incomplete. High CSF flow due to coughing or straining may also result in late onset of CSF leakage due to rupture of a partially healed tear. Dural tears may be enlarged by brain and high amplitude CSF pulsation with resultant erosion of bone.[9,11]

The diagnosis, aetiology, and management of fractures of the orbital roof have been well described by McClachan *et al.*[12] Rhinorrhea is the most common presenting symptom of CSF leakage and presents in 25% of patients with midfacial fracture.[1] Hypo-osmia or anosmia may occur from damage to olfactory nerve fibres in 5% of patients.[9] Smell may be intact in patients who have anteriorly placed frontal sinus fractures or sphenoidal sinus fractures. If fracture of the petrous portion of the temporal bone has occurred, CSF from the middle or posterior cranial fossa may escape into the mastoids and produce middle ear fluid mimicking serous otitis media. Rarely CSF tracks subcutaneously, producing a subepicranial hydroma.[13] Headache occurs in 15% of patients with CSF leakage and is therefore thought to be an inconstant symptom.[9] Meningitis occurs in between 3% and 50% of cases of CSF leakage and the incidence is higher when the leakage is chronic.[11,14–16]

The observant patient may describe a gush of salty fluid, or choke on arising in the morning. In the recumbent position leaking CSF collects dependently in the sphenoid sinus. On the patient's standing, an influx of CSF collected overnight rushes into the oropharynx causing the so-called reservoir sign.[17]

Other signs of CSF leakage include frequent awakening from sleep with coughing fits and soaking of the bed sheets with clear nasal discharge each night. Rhinitis has also been described from chronic CSF leakage.[9,11]

CSF leakage following midfacial fracture in an otherwise asymptomatic patient may be confused with traumatic epiphora. In a series of 300 patients with midfacial fracture where 35% had CSF leakage, 5·3% had concomitant epiphora or dacryocystitis.[5] In a series of 100 patients reported by Campbell with midfacial fracture 12% had complaints of tearing.[18] Naso-orbital trauma may injure the medical palpebral tendon, lacerate or compress the nasolacrimal sac or duct, or cause cicatricial ectropion of the lower lid or punctal malposition.[4,7,8] While CSF leakage usually resolves, dacryocystitis and epiphora commonly persist until surgically treated.

Few cases of chronic CSF leakage into the orbit have been reported in the neurosurgical or ophthalmic literature. In a review of giant epidermoid and dermoid tumors of the orbit Carey described two cases of chronic CSF leakage into the orbit thought to be from direct communication between the subarachnoid space and the inner portion of the tumour.[19] In his series other symptoms including pulsating proptosis, and extraocular movement limitation were also observed.[19]

A case of traumatic CSF fistula simulating epiphora occurred in a child 8 months of age and was reported in the neurosurgical literature.[20] Epiphora occurred immediately following head trauma. The patient presented with coma, hemiparesis, and facial weakness and developed a pulsating exophthalmos accompanied by bruit and chronic epiphora. Chemosis and epiphora resulted from a leak through the ethmoidal sinuses directly to the conjunctiva. The child underwent surgical repair of the fistula soon afterwards.

A case of CSF fistula in a 22-year-old victim of a motor vehicle accident with a cranial nerve palsy has been reported. This patient had a pulsatile right upper lid and chemosis from direct subarachnoid communication with the upper lid. No tearing was observed at any time.[21]

The present case of CSF leakage differs from the above-mentioned cases and has many interesting and hitherto undescribed features. It occurred chronically and continuously in an awake and alert child for a period of three years following injury. Proptosis, chemosis, or eyelid swelling were not noted at any time, and neurological deficit did not develop. No pulsations were observed. Finally, tearing was not suspected to be secondary to orbital CSF leakage until after successful lacrimal drainage surgery had been performed.

CSF leakage occurred as a result of dacryocystorhinostomy surgery in two cases reported by Neuhaus and Baylis and may occur if bone removal extends to the level of the cribriform plate.[22] The same authors noted an average of 5 mm between the nasal ostium and the floor of the anterior cranial fossa.[22] While it is possible that in the reported cases DCR surgery could have created a CSF leak, it is unlikely. Tearing was chronic prior to surgery and persisted after surgery, and it promptly resolved following neurosurgical repair of the posterior orbital encephalocele. Other unlikely hypotheses that might explain the findings in the presented case include the possibility that CSF leaked from the canaliculi in retrograde fashion from the abnormality of the cranial vault, simulating tearing. The CT evidence for this theory is lacking, as the encephalocele was well posterior to the lacrimal drainage system. While remanipulation of a traumatically altered orbit and cranial base undoubtedly introduced meningeal infection, the pathway of CSF leakage from posterior orbit to the tear film is a matter of speculation.

Reagent strips such as Dextrostix and Labstix commonly used for urine glucose determination, while not helpful in distinguishing CSF from nasal discharge,[12 23-26] may be helpful in diagnosing CSF leakage into the orbit. CSF glucose is approximately 70% of that of serum glucose. Normal levels of glucose in tears are insignificant.[26 27] For the purposes of the clinical examination in the reported case, tear concentration in 20 normal individuals without diabetes mellitus was measured with a Labstix reagent strip by placing it directly on the tear meniscus and waiting until wetting had occurred. After 30 seconds the glucose level was measured by matching the colour of the paper with the colour of the glucose as determined on the table found on the bottle. In all patients the glucose level was found to be within 0 and 100 mg/dl (0 and 5·6 mmol/l). In the case described here the glucose level on the uninvolved side was from 0 to 100 mg/dl, corresponding to the normal value. On the involved side the tear glucose level was between 100 and 180 mg/dl (5·6 and 10·0 mmol/l). The higher glucose level on the involved side in this patient was confirmed by laboratory analysis. A large sample needs to be collected for glucose concentration to be analysed in a laboratory. The reagent strips are inexpensive, immediate, and require substantially less tear volume and were effective in diagnosing the leakage.

The site of CSF leakage may be localised radiographically with or without the aid of contrast material. Skull films may show an air fluid level in the sinuses.[9] Materials can be instilled intrathecally to demonstrate leakage of CSF. Methylene blue and fluorescein were at one time injected but have been abandoned owing to numerous complications.[11 28 29] Radioiodide labelled serum albumin and technetium are used to directly visualise CSF leak with cisternography and are diagnostic in 86% of cases.[30-33] Metrizamide encephalocisternography with high resolution CT is mandatory in evaluation of the patient with a suspected chronic orbital CSF leak. In our patient CT scans with axial views were obtained at the time of the original trauma and repeatedly thereafter to evaluate brain, orbits, and skull base and were all within normal limits. One week following DCR axial CTs again did not show any abnormality of the skull base or orbital roof. However, coronal CTs with 1·5 mm cuts clearly show a posterior bony defect and suggested meningoencephalocele and chronic CSF leak. The different perspective offered by directly formed coronal views may be an asset in considering the possibility of chronic CSF leakage into the orbit.

When a CSF leak is noted in the early period post midfacial injury, opinions are varied as to whether direct and immediate reduction of facial fracture or repair of dural tear is indicated. Most authors recommend bed rest with the head of the bed raised. Prophylactic antibiotics are administered intravenously. Bed rest, stool softeners, and medication to prevent coughing or straining are recommended. A lumbar drain, placed in the lumbar subarachnoid space, may be useful in lessening CSF flow through the dural rent, thus allowing repair to take place. Likewise, acetazolamide may be administered to decrease the production of CSF.

The majority of CSF leaks heal without the need for surgery.[9 11] When the neurological condition has stabilised, fractures may be reduced with the realisation that additional trauma to the dura may result.

The treatment of chronic persistent CSF leak is neurosurgical.[11 16 17] If meningitis has supervened, an adequate period of time should elapse for the patient to be on appropriate antibiotics. Chronic CSF leaks usually do not subside spontaneously. The area of the dural rent must be localised and repaired. In the reported case a frontal craniotomy with exposure of the fracture site, Silastic roof implant, and epicranial duroplasty were performed. The techniques of this neurosurgical procedure go beyond the scope of this paper.

Patients who tear after naso-orbital trauma must be suspected of having a CSF leak even if signs of nasolacrimal duct obstruction are present. It may be useful to ask patients specifically about rhinorrhoea or anosmia, as well as to examine for increased tearing during the Valsalva manoeuvre. CT scans should be reviewed if they have been performed and coronal sections are preferred. Finally, Dextrostix can be used to obtain an objective measurement of tear sugar level in order to diagnose chronic orbital CSF leak. If CSF leak is a possibility, the patient should be referred for neurosurgical consultation prior to any lacrimal surgical intervention.

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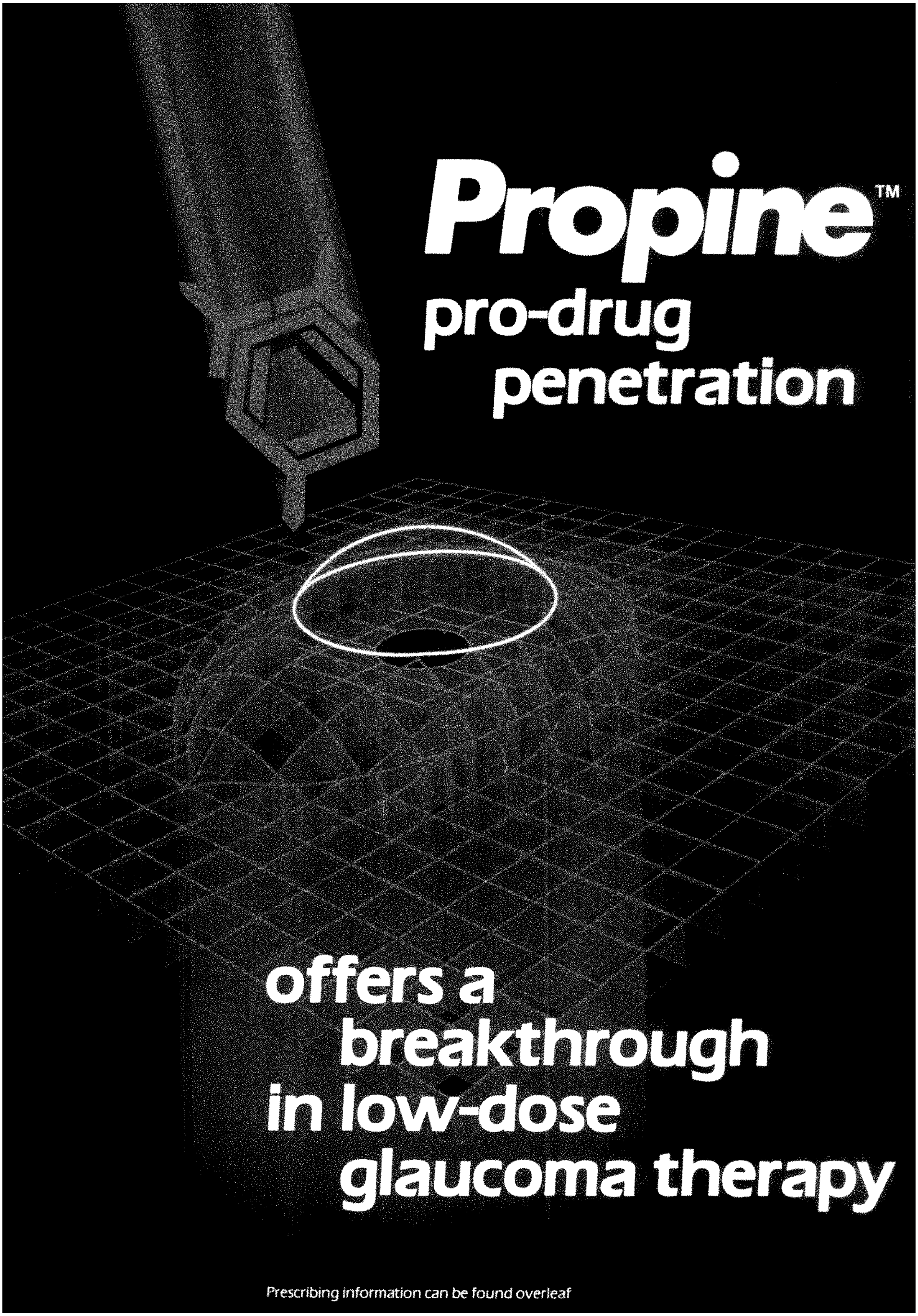

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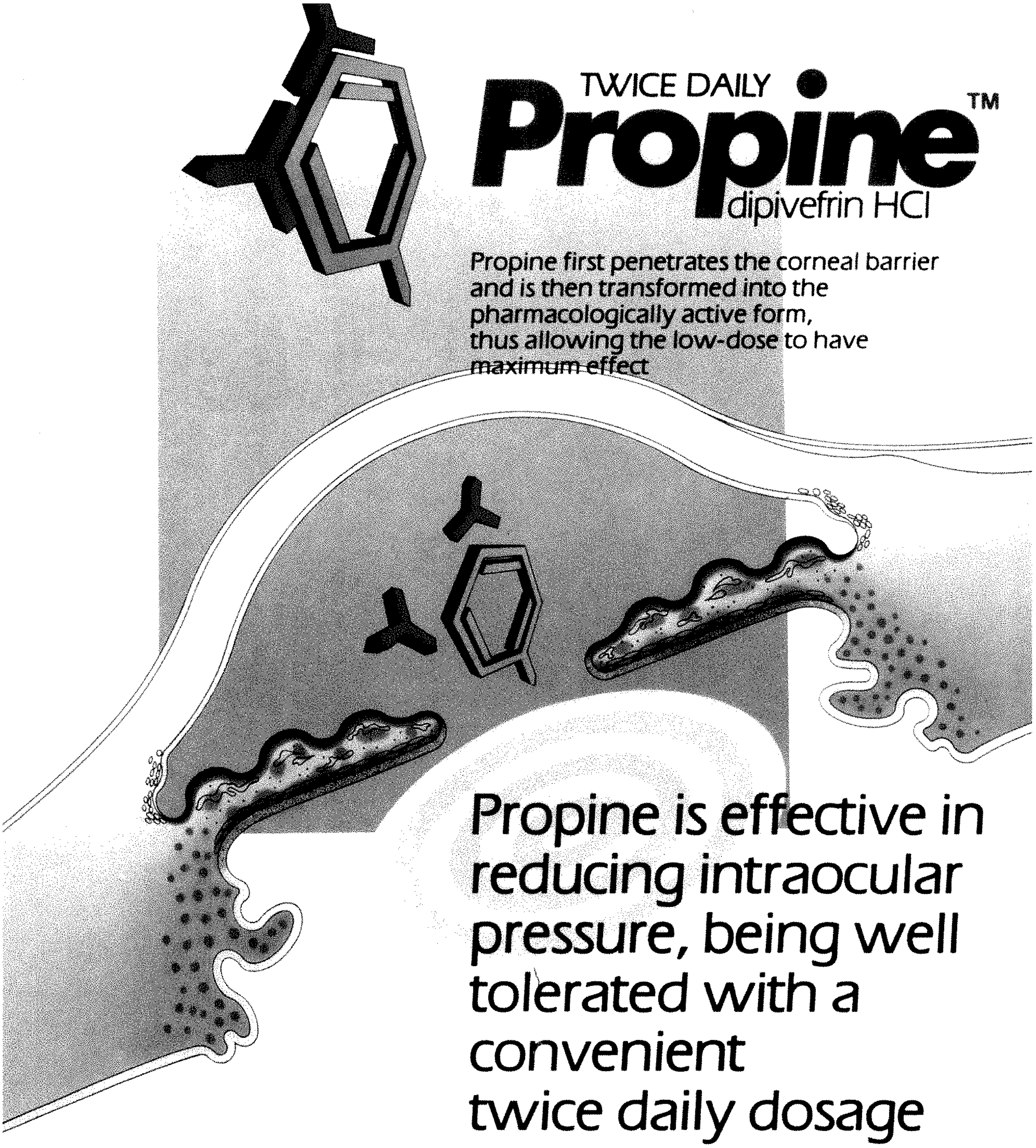

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Surgical management of upper lid entropion

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SUMMARY One hundred and eighty-three surgical procedures were conducted on 107 patients over seven years. 91% of the cases of upper lid entropion were corrected satisfactorily with only one operation. It is postulated that this level of success is achieved by grading the degree of surgical intervention according to the clinical criteria established on systematic examination of upper lid entropion.

The lid malposition of upper lid entropion has many causes. The constant factor regardless of cause is a relative shortage of posterior lamellar lid tissue, comprising tarsus, conjunctiva, and lid retractors, in comparison with the anterior lamella of skin and orbicularis muscle. Many surgical procedures have been devised to manipulate the abnormal anatomy to try to recreate a healthier lid capable of maintaining a healthy corneal environment.[1] Unfortunately the definitive operation does not exist. The policy adopted at Moorfields Eye Hospital, London, was to try, by detailed clinical examination, to gain information on each case of upper lid entropion and adapt an already established operation to its treatment. The assumption was that the surgical principles already advocated were correct but that the variety of pathological lesions encountered created differing amounts of distortion in the tissues. It is well recognised that mucocutaneous cicatricial disease such as trachoma and erythema multiforme (Stevens-Johnson syndrome) causes upper lid entropion of varying degree. Other infective and degenerative conditions also feature as primary pathological lesions, and their effect on the lids is equally variable.

Surgical technique has been previously reviewed, and these established principles were used when attempting to correct the observed deformation of the upper lids.[1] Grading the entropion was conducted by detailed attention to the position of the meibomian gland orifices, conjunctivalisation of the lid margin, the position and direction of the lashes, palpable and visual assessment of the tarsal plate, and the presence or absence of keratin deposits on palpebral conjunctiva.[2]

Patients and methods

A total of 107 patients were reviewed and 183 surgical corrections of upper lid entropion were carried out. The patients were not all domiciled in the United Kingdom and this is reflected in the list of pathological causes of the upper lid entropion (Table 1). The clinical assessment of each case required a standard clinical history plus detailed lid examination (Table 2).

Minimal entropion was defined by posterior migration of the meibomian gland orifices, minimal or incomplete conjunctivalisation of the lid margin, and lashes touching the globe on up-gaze. This pathological change was treated by the limited intervention of anterior lamellar repositioning (Fig, 1), The eyelid was incised and entered along the skin crease, tarsal plate was then exposed and skin undermined distally but stopping 2 mm short of the lash roots. Three or four long-acting absorbable sutures (metric size 6·0)

Table 1 *Aetiology of upper lid entropion*

Diagnosis	*Number of lids*
Trachoma	73
Chronic blepharoconjunctivitis	41
Erythema multiforme	14
Chemical/radiant trauma	12
Postoperative ptosis repair plus tumour excision	9
Pemphigoid	7
Mechanical	7
Postenucleation socket syndrome	6
Herpes zoster ophthalmicus	5
Cicatricial vernal conjunctivitis	5
Dysthyroid	4
Total	183

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Table 2 *Management of upper lid entropion*

Degree of entropion	*Clinical signs*	*Operation procedure*
Minimal	Apparent migration of meibomian glands Conjunctivalisation of lid margin Lash/globe contact on up-gaze	Anterior lamellar ± lid split at grey line (Fig. 1)
Moderate	Apparent migration of meibomian glands Conjunctivalisation of lid margin Lash/globe contact in primary position Thickening of tarsal plate Lid retraction	Anterior lamellar reposition + lid split + tarsal wedge resection (Fig. 2) or Lamellar division (Fig. 3)
Severe	Gross lid distortion Metaplastic lashes Presence of keratin plaques Lid retraction causing incomplete closure	Rotation of terminal tarso-conjunctiva and posterior lamella advance (Fig. 4), or Rotation of terminal tarsoconjunctiva and posterior lamellar graft (Fig. 5)

were used to anchor the skin from just above the lashes to approximately 6 mm up the tarsal plate. Pulling these taut repositioned the anterior lamella and everted the lashes. Further eversion was achieved by splitting the lid margin at the grey line to a depth of 2 mm if this was considered necessary. The skin was then closed with 6·0 collagen, an anchoring point for each suture being taken in the deep tissues of the wound, with incorporation of the lid retractor complex. The resultant fibrosis transmits the upper lid retractor pull to skin, helping to create a good skin crease, and increases the amount of lash eversion, especially on up-gaze.

Moderate entropion was diagnosed when, in addition to the early changes detailed above, there was either lash-globe contact in the primary position or thickening of the tarsal plate. Surgical management of this stage of entropion can also be by anterior lamellar repositioning as described above, including the lid splitting procedure. However, if the tarsus is thickened, as it usually is in trachoma, a tarsal wedge resection can be performed as well. In this procedure a horizontal wedge-shaped defect was cut along the length of the tarsus. The lid-everting sutures that anchor lid skin high on the tarsal plate were placed on either side of the defect in such a manner that, when pulled taut, closure of the defect was attained (Fig. 2).

In addition to the structural distortion of the lid margin in this degree of entropion there can also be lid retraction. This is caused by a relative shortage of posterior lamella compared with anterior lamella due to cicatricial change in the tarso-conjunctival layer. To allow the posterior lamella to advance behind the anterior lamella the procedure of anterior lamellar repositioning and lid split was expanded to include dissection of levator aponeurosis and Müller's muscle from the tarsal plate and conjunctiva. The tarso-conjunctival layer was then advanced. Alternatively, when lid retraction was quite marked, a lamellar division was required. In this procedure the anterior and posterior lamellae were separated by an incision along the grey line of the lid margin. The plane of dissection was then continued up the tarsal plate until

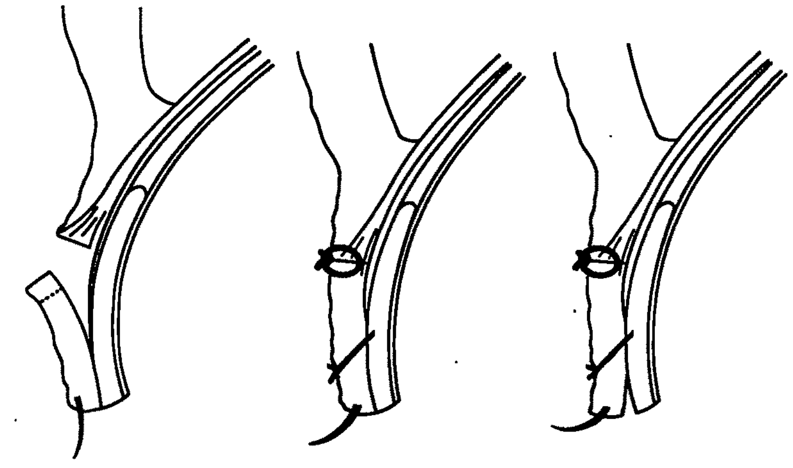
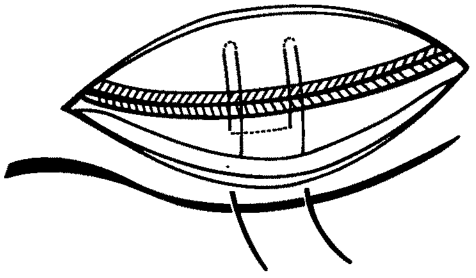


Fig. 1 *Anterior lamellar reposition and lid split*



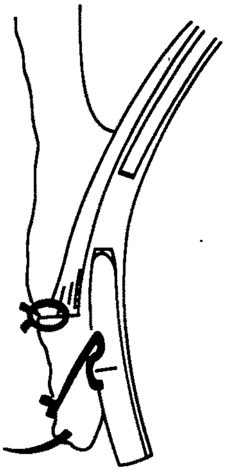


Fig. 2 *Anterior lamellar reposition, lid split, and tarsal wedge resection.*

the anterior insertion of the levator aponeurosis was dissected free from the tarsus. The surgical plane gained was between aponeurosis and Müller's muscle. The latter was dissected from the top of the tarsal plate and underlying conjunctiva, which then allowed the posterior tarso-conjunctival layer to be advanced. The lamellae were then held in position by using three double-armed 4·0 (metric size) absorbable sutures, such as collagen, which were passed through the lid from conjunctiva to skin. A 6·0 (metric size) suture was used to close the wound edge between anterior lid margin and advanced tarsus. The bare area of exposed tarsus was covered with an autogenous graft of mucous membrane as depicted or left to granulate and heal by secondary intention (Fig 3).

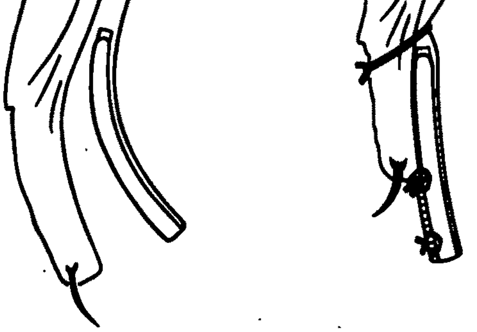


Fig. 3 *Lamellar division with mucous membrane graft covering the exposed tarsus.*

A more severe lid disturbance can be manifest as a totally disorganised margin with metaplastic lashes and trichiasis, definite or gross lid retraction, and keratin formation in plaques on the palpebral conjunctival surface. This last pathology is an inconsistent finding, but its presence restricts the choice of surgical procedure. Regardless of imposed constraints, surgery must be concentrated on the posterior lamella. A lamellar division may be suitable if no keratin deposits are present on the posterior lamella, but often more radical surgery is required. Alternatives that were used in treating these severely distorted lids were the procedures that require rotation of the distal tarso-conjunctiva, which forces any metaplastic lashes or keratin deposits to face away from the cornea.[34] An incision was made across the posterior surface of the lid 3 mm from the inner margin, cutting through tarsus. Once the plane between anterior and posterior lamellae was exposed, dissection proceeded as in the lamellar division. Tarsus and conjunctiva were advanced and held in position by through-the-lid 4·0 collagen sutures, and the distal portion of tarso-conjunctiva was rotated through 180° and sutured directly to the front surface of the advanced raw tarsal plate (Fig. 4). If the tarso-conjunctival layer would not advance sufficiently, a posterior lamellar graft was inserted between the two cut edges of tarsus (Fig. 5). The distal fragment in this case needed only to be rotated through 90°. Graft material was usually autogenous auricular cartilage, but other materials were also used such as buccal mucous membrane, nasal septal cartilage, and stored sclera, and in some unilateral cases tarsus from the opposite healthy lid was used in preference to the foregoing alternatives.[24]

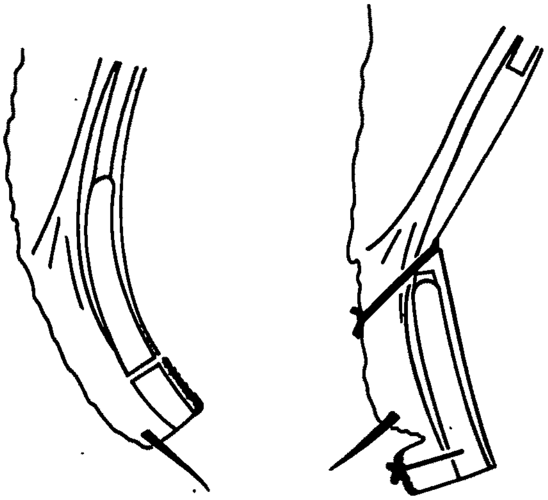


Fig. 4 *Rotation of terminal tarso-conjunctiva containing keratin plaques and posterior lamellar advance.*

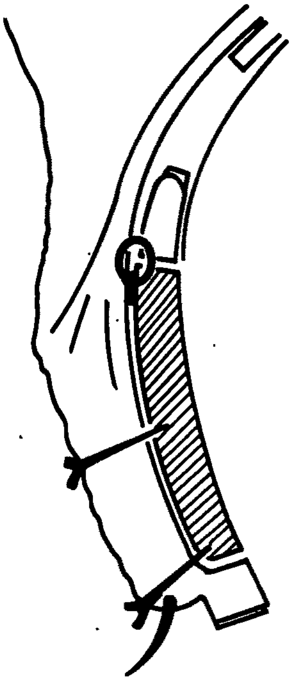


Fig. 5 *Rotation of terminal tarso-conjunctiva and posterior lamellar graft of auricular cartilage.*

Results

The causes are listed in Table 1. There was a disproportionately high number of cases in which trachoma dictated the need for surgical correction–40%. This reflected the international and tertiary referral pattern of patients at this hospital. The next largest group, which was composed mainly of London's indigenous population, was chronic blepharoconjunctivitis–23%. The remaining groups were made up of small numbers of cases. Fourteen operations were carried out on patients suffering from erythema multiforme, and 12 were on patients that had been subjected to some form of trauma. Only nine cases were considered iatrogenic in that they followed ptosis surgery or upper lid reconstruction. The seven operations on cases with mechanical causes were a combined blepharoplasty and anterior lamella repositioning, and these were due to dermatochalasis. Four operations were performed on patients with dysthyroid ophthalmopathy.

Of the 183 surgical procedures carried out only 17 required further surgical intervention. This is a recurrence rate of 9% over a seven-year period with a mean follow-up time of three years, the minimum follow-up period being just 10 months on six occasions. A recurrence was classified as a return of symptoms plus clinical evidence of further lid distortion resulting in lash inversion or corneal epithelial change. All cases were reviewed at least once in the first postoperative year, and none of the recurrences occurred within the first nine months postoperatively. Thus the initial surgical procedures did not appear faulty: 36 operations were followed by further attention to aberrant or metaplastic lashes by means of electrolysis or cryotherapy (Table 3). Forty patients have been fully discharged, and, of the remaining 67 under continuing outpatient review, 43 are using topical lubrication of methylcellulose or polyvinylpyrrolidone (Table 4).

Table 3 *Results of upper lid entropion surgery*

	No. of operations conducted	*No of recurrences*	*No. of lids with aberrant lashes postoperatively*
Group A	94	10	20
Group B	.49	5	8
Group C	40	2	8

Table 4 *Disposal of patients*

Discharged and no topical therapy	*Regular follow-up*	*Using topical therapy in regular follow-up*
40	67	43

Discussion

The range of pathology associated with upper lid entropion in this study is interesting. There are the two large groups of trachoma and chronic blepharoconjunctivitis, but in addition it is of interest to note the less common conditions. Dermatochalasis and dysthyroid ophthalmopathy are examples of conditions usually associated with other lid signs and other more specific operative procedures. Patients with ocular pemphigoid, although representing a large clinical group, were not subjected to many entropion repairs, as the condition is rarely static enough to consider surgical intervention as definitive treatment. In some severe cases of vernal conjunctivitis there appeared to be enough residual fibrous contraction to precipitate a frank entropion requiring repair. Usually herpes zoster ophthalmicus is associated with cicatricial ectropion, but a small group of lids developed the opposite problem, requiring attention to an entropion. The other four pathological groups of erythema multiforme, chemical/radiant trauma, postoperative entropion, and postenucleation socket cases were less unusual and could be anticipated as potential sources of surgical material.

In considering the efficacy of surgical intervention it is important to be aware that in most cases the primary pathology is unfortunately not at an end stage when the first surgical procedure is necessary. What has been shown by the 9% recurrence rate is that it is possible to alter a lid's response of entropion to a variety of pathological causes by graded surgical intervention. It would appear that in 91% of cases it is possible satisfactorily to influence lid position in order to create a healthy corneal environment, which is the main victim when entropion exists. Most of the causes of cicatricial mucocutaneous disorders affect the goblet cells and accessory lacrimal glands. Therefore it is gratifying that after surgery most tear films appear clinically to improve, but more specifically 60% of patients postoperatively require no artificial addition to what basic tear production they possess (Table 4).

In the past various authors have advocated a specific definitive entropion correction, and the current history of entropion repair dates from the mid-nineteenth century.[3,5-7] In this department the established surgical principles and procedures have been accepted but modified. After systematic clinical assessment the pathological change in an upper eyelid is graded, and an appropriate but usually limited operation is then devised to suit the circumstances. This approach would appear to be justified by the success rate recorded in this retrospective study. The lowest recurrence rate was in the group where the most radical surgery was performed. This probably reflects not only the efficacy of technique but that the most gross lid disturbance will be at the end stage of the pathological process, so that little or no progression of cicatrisation will occur. No distinct pathological cause appeared to be prevalent in the patients requiring further attention to individual lashes or small numbers of recurrent or metaplastic lashes. The method of removing these by either cryotherapy or electrolysis was not solely dictated by the operator's preference but also by surrounding circumstances. Lids that had either graft material in the posterior lamella or a substantial amount of normal lashes had electrolysis performed to remove aberrant single lashes, whereas if the lash population was of poor quality and no graft had been used then cryotherapy was employed.[8]

Electrolysis was also preferred when dealing with pigmented lids, as there was no risk of the cosmetically distressing pigment loss that may occur when using cryotherapy. Both methods were used, overall, an equal amount and with similar success.

This retrospective study does not present any new surgical procedures but tries to apply established techniques in an ordered fashion. It is considered that the systematic approach of clinical analysis influencing surgical procedure has been vindicated. The criteria detailed earlier are regularly identified either by naked eye or with the slit-lamp biomicroscope. As such the clinical assessment allows consistency in grouping lids according to deformity and in so doing indicates the best possible surgical approach for repair of upper lid entropion.

We are grateful to Churchill Livingstone for kind permission to reproduce the diagrams; the Medical Illustration Departments of Moorfields Eye Hospital and University of Dundee Medical School; and Miss E C Garner for secretarial services.

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Eccrine spiradenoma of eyelid: case report

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SUMMARY A case report is presented of eccrine spiradenoma, a benign sweat gland tumour which, though not uncommon generally, is rare in the eyelid. The possibility of sweat gland tumour should be kept in mind in the diagnosis of eyelid tumours.

The eccrine spiradenoma is a benign neoplasm of the skin first described by Kersting and Helwig,[1] who considered it to be a derivative of eccrine sweat glands. It usually presents as a solitary, intradermal, and painful nodule, the commonest sites being the chest and face.[1] In the available literature we could find no case of eccrine spiradenoma of the eyelids. The following case report may therefore be the first from India.

Case report

A 55-year-old female presented in June 1984 with a nodule in left upper lid for the last two and a half years, which had been gradually increasing in size. It had ulcerated six months previously, causing pain and bleeding. The swelling measured 2·4 × 2 × 1·2 cm and involved lateral half of the left upper lid (Fig. 1). The growth was firm to hard in consistency and tender to touch. In an area 1 cm × 0·6 cm near the lid margin, including anterior half of the lid margin, the swelling was ulcerated. The margins of the ulcer were undermined, and the floor showed healthy granulation tissue.

An ophthalmic examination revealed nothing abnormal except for early lenticular opacities, and the patient's vision was 6/18 in both the eyes. A general physical examination also showed nothing abnormal. There was no enlargement of auricular, cervical, or submandibular lymph nodes; the liver and lungs were normal.

Clinically an epithelioma of the eye lid was suspected, and a full-thickness wide excision of the left upper eyelid including the growth was carried out under local anaesthesia. Reconstruction of the upper lid was from a lower lid flap by the technique suggested by Cutler and Beard.[2] Figs 2 and 3 a, b show the first and second stages of the reconstruction operation.

BIOPSY REPORT

Gross description. The specimen submitted to the pathology department comprised a portion of excised lid and surrounding soft tissues measuring together 3·0 × 2·5 × 1·4 cm. The overlying skin revealed an ulcer which measured 1·0 cm × 0·5 cm and was skin thickness deep. On palpation a mass could be felt beneath the skin. Bisection revealed a lobulated and circumscribed tumour underneath skin which measured 2·2 × 1·8 × 1 cm. It was grey-white, firm, and had a rubbery surface.

Microscopic description (Figs 4 and 5). Sections stained with haematoxylin and eosin showed a tumour comprising lobules of various sizes in the corium. It had a sharply contrasting deep basophilia

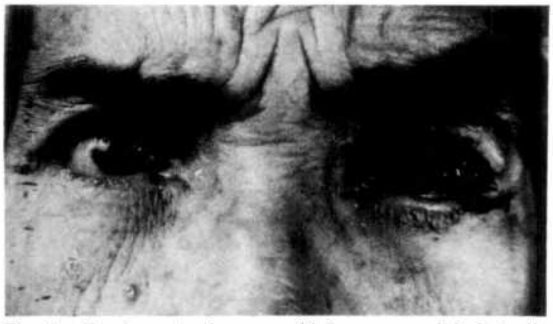

Fig. 1 *Eccrine spiradenoma of left upper eyelid clinically resembling squamous cell epithelioma.*

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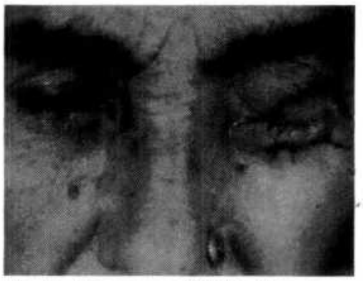
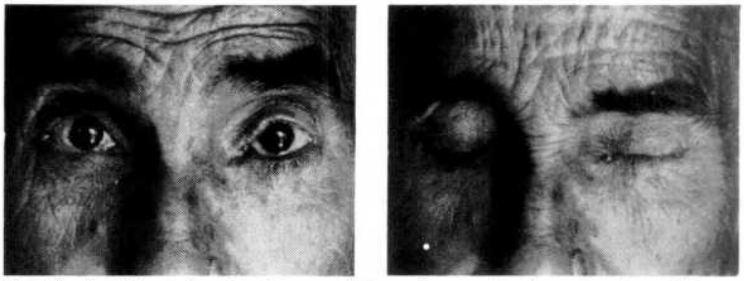


Fig. 2 *First stage of Cutler-Beard procedure for upper eyelid reconstruction.*



Figs. 3 a, b *Six weeks after the second stage of reconstruction procedure with eyes open* (a) *and closed* (b).

and did not connect with the overlying epidermis. The surrounding connective tissue was normal. The parenchymal tumour cells were of two types, arranged mostly in cords, whorls, and pseudoglandular formation. Cells of one type were large, light staining, closely packed, and at places surrounding a central lumen. Cells of the other type were small with compact nuclei, and mainly arranged at the periphery. In general there was insignificant inflammatory reaction within the tumour and the surrounding tissues, but in the area immediately beside and below the ulcer an extensive mononuclear cell infiltrate was noted. The histopathology was suggestive of eccrine spiradenoma.

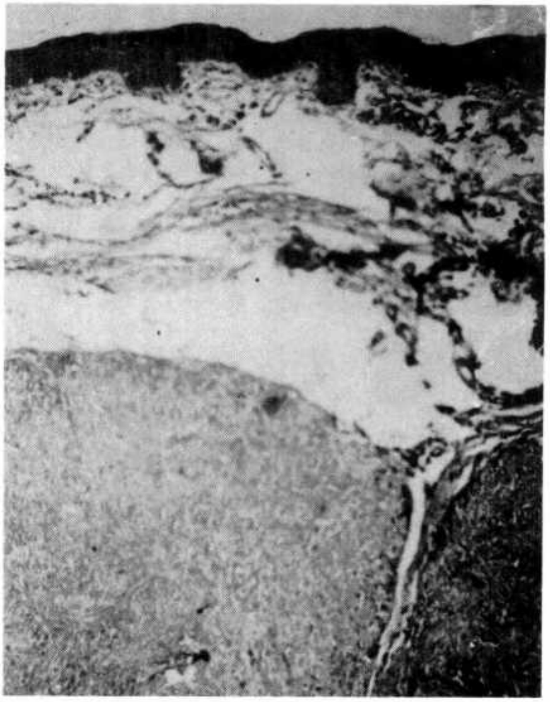


Fig. 4 *Tumour lobules present in the corium, with sharply contrasting deep basophilia (H-E, × 80).*

Discussion

Tumours arising from the sweat apparatus of the eyelid are uncommon, and the differences in their structure have given rise to much confusion. A wide variety of descriptive terms have been applied to them.[1-3] Histologically there are two subdivisions of the sweat glands—eccrine and apocrine. Eccrine glands are present throughout the skin but are most abundant in the palms, soles, and axillae. In the eyelid they are present both at the lid margin and in the dermis over the surface of the eyelid. On the other hand apocrine glands are found in only a few areas, mainly the axillae, round the nipples, and in the anogenital region, with occasionally a few on the abdomen and chest. Apart from these they are present as modified glands in the eyelids, breast, and external ear canal, where they are known as Moll's glands, mammary glands, and ceruminous glands respectively. Kersting and Helwig[1] enumerated six sweat gland tumours without further grouping them according to type or portion of the sweat apparatus involved or the nature of the proliferation. In accordance with the nature of the growth Lever[4] classified sweat gland tumours into four groups—hamartomas, adenomas, benign epitheliomas, and primary epitheliomas—but without taking account of part of the sweat apparatus involved. This was considered by Allen,[5] who divided these tumours into two groups—ductal (syringal) and glandular. These were further divided by eccrine and apocrine differentiation. The eccrine spiradenoma falls into the category of benign epitheliomas according to the classification of Lever[4] and is ductal in origin, being also termed a lobular syringoma.

Whatever classification or nomenclature is adopted, eccrine spiradenoma remains an established clinicopathological entity with a distinct histological appearance. However, the possibility of a primary basal cell epithelioma with eccrine differentiation and a lobular, hyalinised syringoma (cylindroma) should be included in the histological differential diagnosis. The former is identified by a

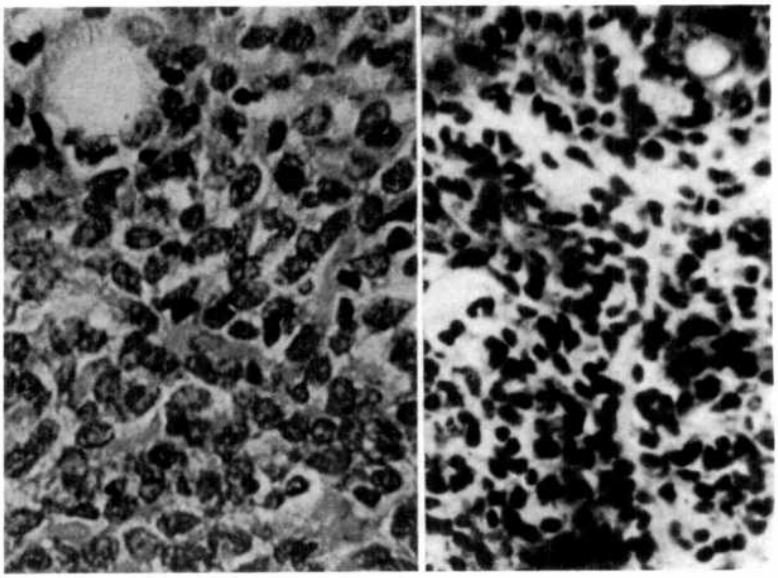


Fig. 5 *Tumour parenchyma under higher magnification. Larger lightly staining cells are closely packed and appear to surround a central lumen (left upper corner). In contrast (right side) smaller cells have compact nuclei and are present at the periphery (H-E, × 650).*

rim of basal cells arranged neatly in a radial pattern strongly reminiscent of the more or less vertically arranged basal cells forming the lowermost layer of the normal epidermis. The latter is characterised by conspicuous hyalinised bands of collagen surrounding and intertwining among the lobules and its cells.

None of these features was seen in the present tumour, which comprised lobules of variable sizes having sharply contrasting basophilia and two types of tumour cells—one large light staining and closely packed, the other with compact nuclei arranged mostly at the periphery. In our case the microscopical picture is consistent with those described by other authors.[1,4-6] Munger *et al.*[6] confirmed the eccrine origin after an electron microscopy of a tumour having a similar light microscopic appearance.

Histochemistry and electron microscopy offer supplementary information. However, the criteria that appear to be decisive in differentiating the normal structures of the sweat apparatus are apparently not always applicable to neoplasms. In general, amylophorylase, branching enzyme, succinic dehydrogenase, and leucine aminopeptidase are regarded as indicative of eccrine ducts and glands, whereas acid phosphatase and β-glucuronidase are stated to be characteristic of apocrine glands.[5] Yet cylindroma, which is clearly of eccrine origin, has been found histochemically by some investigators[4] to suggest an apocrine origin.

Kersting and Helwig[1] and Munger *et al.*[6] state that eccrine spiradenoma usually presents as a solitary intracutaneous nodule, often tender to touch, but occasionally there may be multiple tumours. In our case the clinical presentation as an ulcerated growth is quite different from the description of other workers.[1,6] Consequently a clinical diagnosis of squamous cell epithelioma (a common tumour of the lid margin) was made.

Many classical cases of eccrine spiradenoma have been reported.[1,4-6] However, none of these authors reported involvement of eyelids. Even Kersting and Helwig,[1] who showed eccrine spiradenoma to be a distinct clinicopathological entity in a series of 134 cases, did not find a single tumour arising from the eyelid. However, certain other types of sweat gland tumours, such as porosyringoma[7] and clear cell hidradenoma or myoepithelioma,[8,9] have been reported in relation to eyelids. The rarity of the eccrine spiradenoma at that site made the present case worth reporting.

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Tear and serum antibody levels in ocular herpetic infection: diagnostic precision of secretory IgA

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SUMMARY A sensitive enzyme linked immunosorbent assay (ELISA) was developed to evaluate the potential of herpes simplex virus (HSV) specific antibodies in the diagnosis of herpetic eye infection. The presence of HSV specific secretory IgA (sIgA) in tears was found to be diagnostic of infection. However, serum and tear HSV specific IgG and IgA were not considered reliable indicators of active infection.

Herpes simplex (HSV) virus is an important cause of ocular infection and is acknowledged as a major cause of corneal blindness in developed countries. It is therefore important accurately to diagnose and treat herpetic eye disease. The diagnosis is often made on pathognomonic clinical findings such as corneal dendritic ulcers and less frequently cutaneous lid vesicles.[1] However, herpetic eye infections may present non-specifically as an acute follicular conjunctivitis or punctate keratoconjunctivitis,[2] in which the differential diagnosis includes adenoviral infections and trachoma inclusion conjunctivitis. HSV ocular infection has been estimated to account for 21% of patients attending an ophthalmic casualty department with an acute conjunctivitis.[3]

The laboratory diagnosis of HSV infections is usually made on tissue culture, but this technique depends on the presence of viable virus and may be inhibited by antivirals and antibodies. Alternatively the measurement of HSV specific antibodies has been suggested as a diagnostic parameter.[3-5] However, HSV specific IgG and IgA antibodies in serum are present in the majority of the adult population,[6 7] and levels of antibodies in tears may be falsely elevated by transudation of serum antibodies in to the lacrimal fluid of an inflamed eye.[8] The detection of secretory IgA (sIgA) in tears should avoid these problems, as it is locally produced and is not present in serum.[8] Tear sIgA is a dimeric IgA synthesised by subepithelial plasma cells in the lacrimal gland,[9] which then binds to receptors on epithelial cells and is transported across the cell to the duct.[10] The secretory component in sIgA is derived from the cell receptor and binds to the J chain of dimeric IgA.[10] A radioimmunoassay for sIgA specific to HSV has previously been described,[11] and, although it has not been assessed in a clinical context, the authors considered that the assay had diagnostic potential.[5]

In this paper we describe a sensitive method for the detection of HSV specific antibodies (IgG, IgA, and sIgA) by enzyme linked immunosorbent assay (ELISA) and compare the response in a variety of clinical presentations of HSV ocular infections.

Materials and methods

Fifty-six patients attending the Casualty Department at Southampton Eye Hospital with suspected acute viral conjunctivitis during the period June to December 1984 were included in this study. All patients were examined on a Haag-Streit slit-lamp and were assigned to one of three clinical categories: (i) acute follicular conjunctivitis or keratoconjunctivitis; (ii) corneal dendritic ulcers; and (iii) orofacial herpetic vesicles with a conjunctivitis. Nineteen controls were selected from patients with an inflamed eye not due to infection.

Tear samples from the lower fornices of affected eyes were collected into 0·7 mm internal diameter capillary tubes. These tubes, which contained an inner filament to increase capillarity (Kwik-fil glass capillaries: Clark Electromedical Instruments), were bent into a hockey-stick shape to facilitate collection.

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The sample (usually 5 to 20 µl) was expelled into a preweighed conical plastic tube and transported to the laboratory, where it was diluted with an equal volume of glycerol and stored in liquid state at −20°C. By this method it was usually possible to collect adequate volumes for analysis from an inflamed eye.

Conjunctival swabbings for virus isolation were taken from the lower fornix and placed in viral transport medium (HEPES buffered HBSS containing 10% fetal calf serum and antibiotics). HEp-2 and MRC-5 cells were inoculated, incubated at 37°C, and examined regularly for the presence of cytopathic effect. HSV isolates were identified by electron microscopy.

Blood samples were collected by venepuncture at the first presentation to the Casualty Department. Sera were separated and stored at +4°C with 0·05% sodium azide. All samples were transported to the laboratory immediately after collection.

Serum and tear antibody levels were measured by indirect ELISA. 96-well high activated PVC plates (Flow Laboratories) were coated with excess antigen by overnight incubation with HSV antigen in 0·1 M sodium carbonate buffer, pH 9·6. The antigen was prepared by extraction of HSV type 1 infected Chang conjunctival cells with 1% (w/v) sodium cholate. Serum and tear samples (1 µl) were diluted 1:100 in 5% normal rabbit serum with 0·05% (w/v) Wl detergent (Sigma) and 0·9% NaCl and incubated in the antigen-coated wells for three hours at 37°C. Antigen specific IgG, IgA, and sIgA were detected by anti-IgG, anti-IgA, and antisecretory component horseradish peroxidase (HRPO) conjugates (Dakopatts) at respective dilutions of 1:2000, 1:2000, and 1:100 as above. After 30 minutes' incubation at 37°C the enzyme substrate 3, 3′, 5, 5′–tetramethylbenzidine (TMB, Miles) was added[12] and the reaction allowed to proceed for 5 minutes. The enzyme reaction was stopped by the addition of 2 M H_2SO_4 and the absorbance $_{450\ nm}$ measured (Titertek Multiskan, Flow Laboratories).

Virus specific immunoglobulin G and A concentrations were calculated from a standard curve of absorbance $_{450\ nm}$ plotted against immunoglobulin class. This was constructed by incubation of anti–IgG and anti–IgA HRPO conjugates, as described above, in plates coated with dilutions of purified IgG and IgA radiolabelled with ^{125}I to a known specific activity with the solid phase chloramine-T reagent, Iodobeads (Pierce). The amount of solid phase immunoglobulin standard at each dilution was measured using a gamma counter. Each immunoglobulin class specific conjugate showed no detectable cross reactivity with the other antibody class. This method permitted quantitation of IgG levels over the range 0·2–14·0 µg/ml and of IgA levels in the range 0·5–26·0 µg/ml. (SI conversion: µg/ml=mg/l.)

Secretory IgA levels in tears were expressed in absorbance units, as no purified secretory component was available to construct a standard curve. Values were considered positive if they fell outside 2 standard deviations of the mean background level as measured in the corresponding sera. No cross-reactions with purified IgA, IgG, or IgM could be detected by ELISA.

Results

Clinical presentation. Of the 56 patients included in this study 19 presented with a follicular conjunctivitis or punctate keratoconjunctivitis, 31 with corneal dendritic ulcers, and 6 with an inflamed eye in conjunction with orofacial herpetic vesicles. The 19 controls included 15 postoperative patients (eight cataracts, four glaucoma, three retinal detachment), two traumatic abrasions, one lens induced uveitis, and one glaucoma patient on treatment.

Tissue culture. HSV was isolated from 19 of the 56 patients, of whom 16 had dendritic ulcers, two had orofacial herpetic vesicles with a conjunctivitis, and one had a follicular conjunctivitis.

Serum and tear HSV specific IgG and IgA. HSV specific IgG and IgA was measured by ELISA in serum from 48 patients and 19 controls and in tears from 49 patients and 19 controls. These results are displayed in Fig. 1, analysed by clinical category.

High levels of HSV specific IgG and IgA were detected in sera from all groups, including the controls. Serum HSV specific IgG levels were significantly higher in the dendritic group ($p<0·005$) and the orofacial vesicles/conjunctivitis group ($p=0·0095$) when compared with the controls. Similarly HSV specific serum IgA levels were significantly higher in the dendritic group ($p=0·007$) and the orofacial vesicles/conjunctivitis group ($p=0·004$) than the controls. Both HSV specific IgG and IgA levels in serum were similar in the controls and the follicular conjunctivitis group.

Tear samples from all groups contained HSV specific IgG and IgA with no significant difference between the controls and any of the clinical groups. HSV specific IgG and IgA were never present at higher levels in tears than in the corresponding sera.

Tear antibody levels were analysed by day of presentation among patients in whom either HSV was isolated by tissue culture or sIgA detected. The levels of tear IgA were significantly higher ($p=0·05$) after the second day of symptoms when compared with those presenting earlier. No such rise in tear IgG levels with time could be shown.

HSV specific sIgA in tears. Tear samples of sufficient

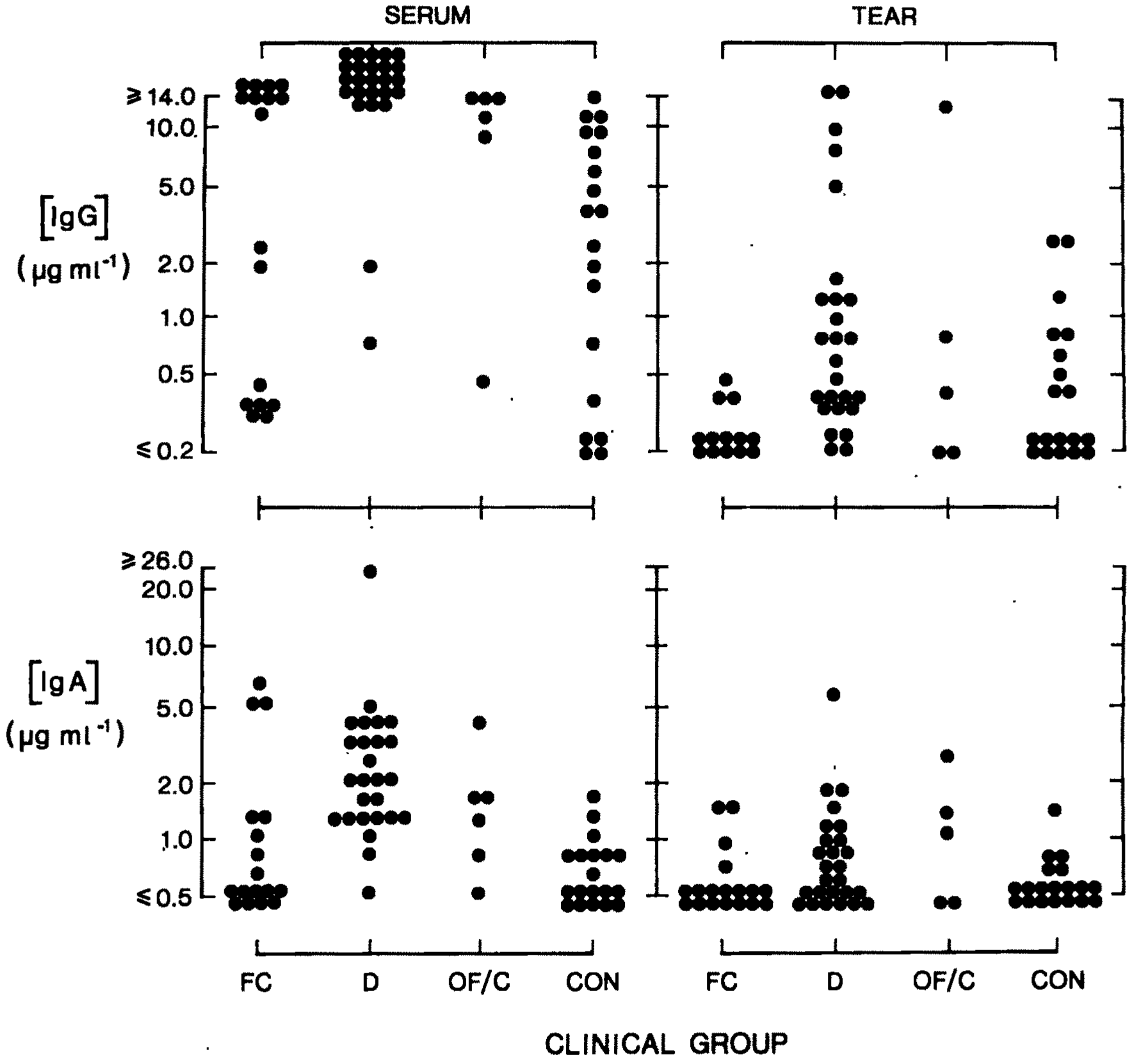

Fig. 1 *Serum and tear levels of HSV specific IgG and IgA analysed by clinical group.* FC=*follicular conjunctivitis.* D=*dendritic ulcers.* OF/C=*orofacial vesicles/conjunctivitis.* CON=*controls.*

volumes to measure sIgA were available from 53 patients and 19 controls. HSV specific sIgA was detected in 20 of the 53 patients, of whom 12 were HSV isolate negative. Secretory IgA was not detected in any of the control group (Fig. 2).

In the dendritic ulcer group 16 out of the 29 tear samples contained sIgA. Of these, 10 were HSV isolate negative by tissue culture. A total of 26 of the 31 patients in the dendritic group were either HSV isolate positive or had detectable HSV specific sIgA. In the orofacial herpetic vesicles/conjunctivitis group tears from three of the six patients contained HSV specific sIgA, of which one was HSV isolate negative. HSV specific sIgA was found in one patient in the follicular conjunctivitis group; this patient was HSV isolate negative.

Secretory IgA levels were correlated against duration of symptoms in 29 patients in whom either HSV was isolated by tissue culture or sIgA was detected (Fig. 3). Fourteen of the 19 isolates of HSV were obtained from patients with symptoms of seven days' duration or less. Of the five isolates with symptoms of more than seven days three had been treated with topical steroids prior to presentation to the Eye Hospital. Eight patients with no detectable sIgA were HSV isolate positive. Of these, seven presented

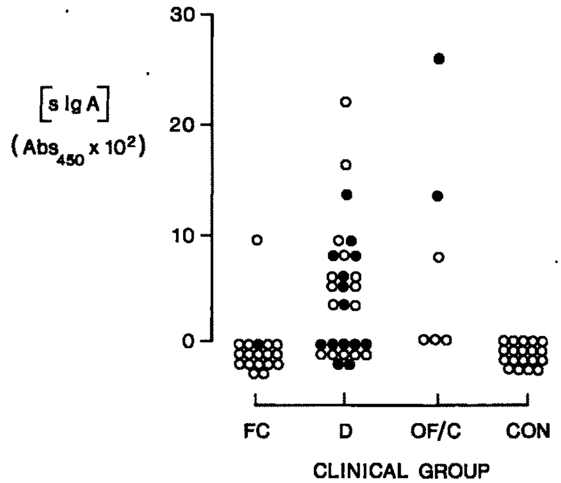

Fig. 2 *HSV specific secretory IgA (sIgA) levels in tears analysed by clinical group.* FC=*follicular conjunctivitis.* D=*dendritic ulcers.* OF/C=*orofacial vesicles/conjunctivitis.* CON=*controls. Cases showing positive (●) or negative (○) virus isolation.*

in the first four days of symptoms and one presented at day 14 but had received topical steroids prior to presentation.

Follow-up tear samples, taken from six to 30 days after the first sample, were available from seven patients. Six of these samples contained HSV specific sIgA on presentation and remained detectable on follow-up. Two of these patients were HSV isolate positive on presentation, but tissue culture was consistently negative on follow-up. One tear sample taken at day 42 from a patient with a healing dendritic ulcer contained sIgA, but HSV was not isolated (Fig. 3).

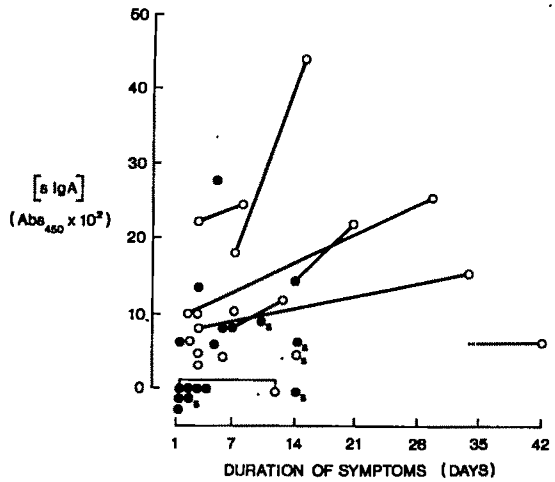

Fig. 3 *Analysis of HSV specific secretory IgA (sIgA) levels in tears according to duration of symptoms at presentation and on follow-up (paired values). One unpaired convalescent tear sample was obtained at day 42. Positive or negative virus isolation denoted by (●) or (○) respectively. s=Prior application of topical steroids.*

Discussion

In this study HSV specific sIgA was detected in the tears of 19 of the 37 patients with characteristic herpetic lesions (dendritic ulcers or orofacial vesicles/conjunctivitis). In contrast none of the controls and only one of the 19 patients with a follicular conjunctivitis had detectable HSV specific sIgA in their tears. This suggests that the presence of HSV specific sIgA is indicative of herpetic infection. Secretory IgA was generally detected only in patients presenting after the first few days of symptoms, from whom HSV was usually not isolated on tissue culture. The detection of HSV specific sIgA in conjunction with virus isolation increased the laboratory diagnosis of HSV eye infections to 55% of the patients in our study, compared with 34% by tissue culture alone. In particular a laboratory diagnosis of HSV infection could be made in 84% of the dendritic ulcer group.

Although levels of HSV specific serum IgG and IgA were significantly higher in both the dendritic ulcer group and the orofacial vesicles/conjunctivitis group than in the control group, the presence of high antibody levels in some controls with no evidence of herpetic eye infection indicates that these parameters are not diagnostically reliable. The rise in tear IgA levels, though not IgG, presumably reflects local production of sIgA. However, the overall similarity in tear IgA and IgG levels between the clinical groups and the controls confirms earlier suggestions that these values are not diagnostic, possibly owing to transudation of serum antibodies. The detection of tear IgG and IgA in over half of those controls with detectable serum antibodies is evidence of transudation of antibodies into an inflamed eye.

Four patients with a laboratory diagnosis of HSV infection had low levels of serum IgG specific to HSV on presentation, which suggests that these were primary herpetic infections. Two of these patients had dendritic ulcers, which may develop in primary herpetic eye infection,[2] and two presented with a follicular conjunctivitis. A follow-up serum sample in one of the patients with a dendritic ulcer showed a rise in levels of HSV specific IgG (from 1·5 to 9·0 µg/ml), which was associated with a concurrent rise in HSV specific IgM (from 4·5 to 7·0 µg/ml). (SI conversion: µg/ml=mg/l.)

Four patients presented with corneal dendritic ulcers following the use of topical steroids, which are known to enhance dendritic ulceration.[13] It is of interest that these patients had lower sIgA levels, and HSV was isolated later in the course of the disease, in comparison with the rest of the patients with evidence of active HSV infection.

We conclude that the detection of HSV specific tear sIgA by ELISA in patients with suspected viral conjunctivitis is a valuable adjunct to virus isolation in the diagnosis of herpetic eye infection. HSV is usually isolated in the first few days of symptoms, when sIgA levels are low. The rise in HSV specific sIgA thereafter permits a laboratory diagnosis to be made when virus is usually not recovered on tissue culture, in particular following the use of antivirals. The detection of HSV specific sIgA by enzyme linked immunosorbent assays provides a rapid and sensitive diagnostic assay without the need for expensive laboratory equipment or radioisotope handling facilities.

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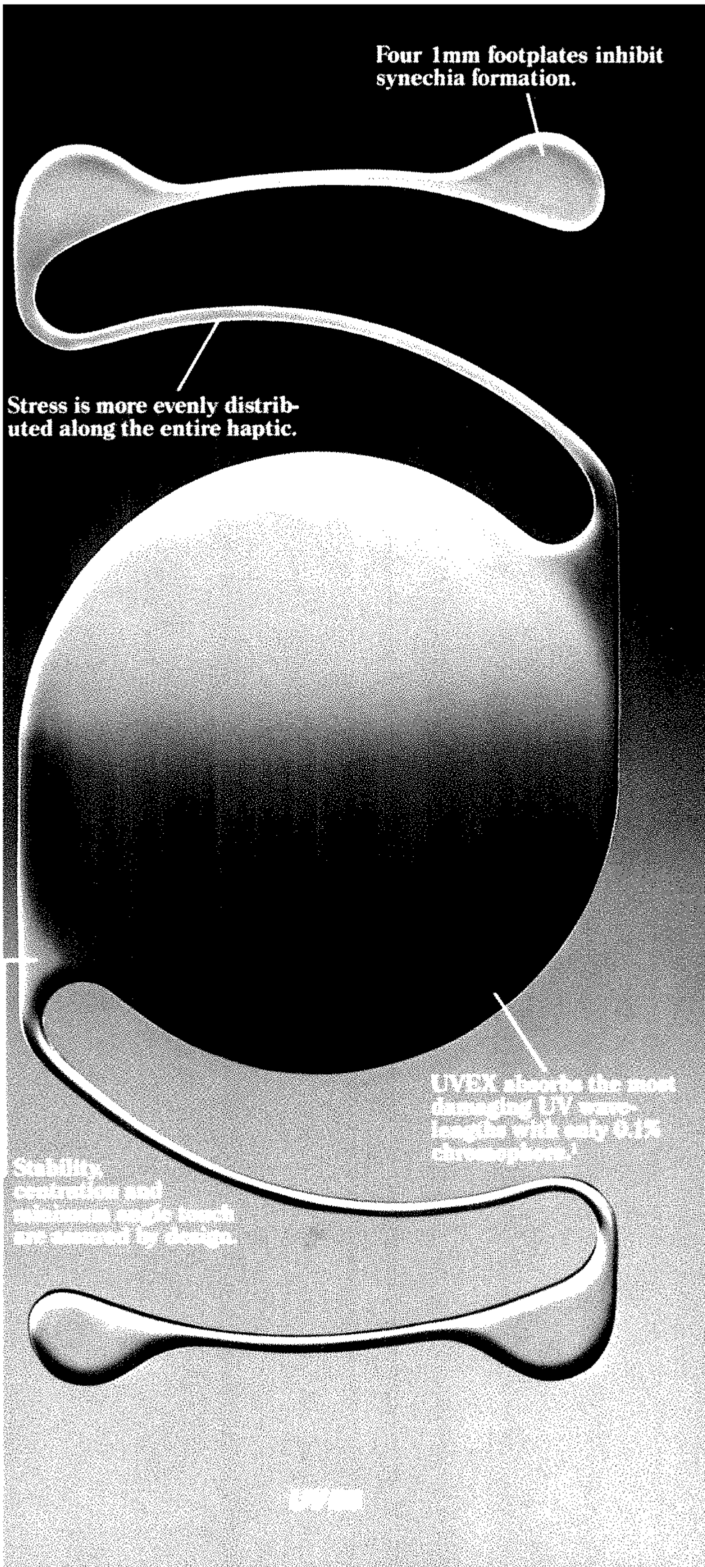
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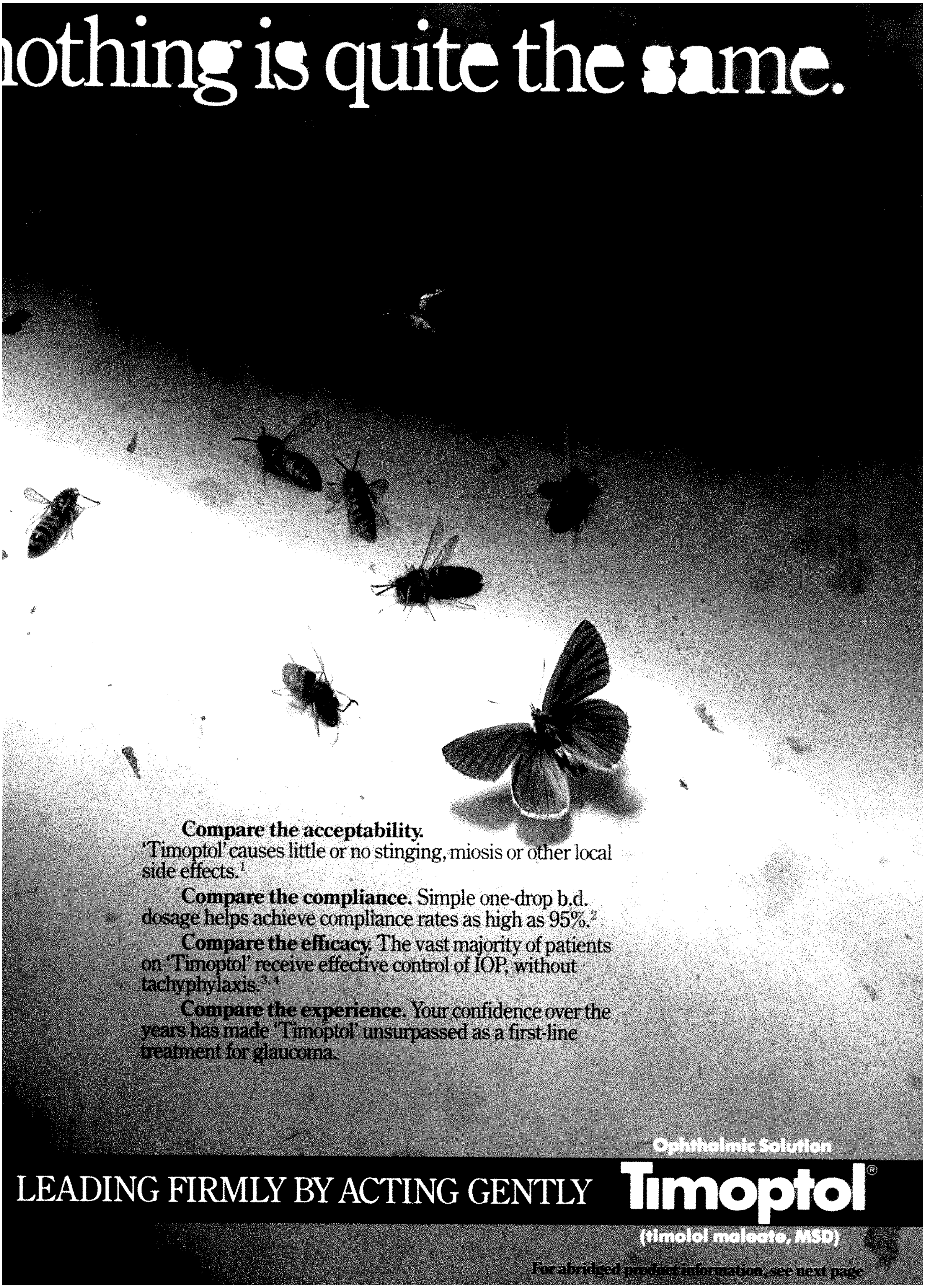
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Treatment and visual prognosis in Behçet's disease

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SUMMARY For the last decade we have observed and regularly followed 49 patients with the ocular type of Behçet's disease. Thirty-six patients were males and 13 were females. Regardless of whether the initial ocular presenting symptoms were in the anterior or posterior segment, both segments were involved within two years. Sterile hypopyon was recorded in 17 out of the 49 patients during the process of follow-up. In three of the patients hypopyon was the presenting symptom. Characteristically there was a lack of corneal or scleral involvement in the disease process. All patients responded initially to treatment with steroids, but 42 had a course of treatment with cytotoxic-immunosuppressive drugs for various lengths of time after 'resistance' to steroids developed. Although definitely effective in reducing the intensity of the ocular inflammatory processes, it is not clear yet whether these modes of treatment have any dramatic effect of the visual prognosis of the affected eyes. Despite intensive follow-up and treatment, loss of useful visual acuity has occurred in 74% of the eyes six to 10 years after the start of the ocular symptoms.

Probably identified already by Hippocrates[1] and clinically described in a few reports early this century,[2-5] Behçet's disease was recognised as a clinical entity only in 1937.[6] Though originally described as a disease manifested by aphthous stomatitis, genital ulcers, and visual disturbances (the classical triad), it soon became evident that Behçet's disease is not confined only to the above organs.[7-9] Because of the multisystemic manifestations, confusion over the criteria for diagnosis and the incidence of involvement of the various organs had developed. Thus the incidence of ocular manifestations varies from 23% to 96% of cases whether the report originated from a dermatology[10] or ophthalmology[11] department. Aware of these possible biases, we have been classifying Behçet's disease as ocular type when the classical triad of symptoms is observed and non-ocular type if the diagnostic criteria as suggested by the Behçet's Syndrome Research Committee of Japan are met[12] but the eyes are not involved. We report herein our observations on the treatment and visual prognosis of the ocular type of Behçet's disease during the last decade.

Correspondence to Professor D BenEzra, Department of Ophthalmology, Hadassah University Hospital, PO Box 12000, 91120 Jerusalem, Israel.

Materials and methods

PATIENTS

During the decade 1975–85, 70 patients with the diagnosis of Behçet's disease were examined in our clinic. Twenty-one patients did not meet the criteria for the ocular type of Behçet's disease. Forty-nine had aphthous stomatitis, ulcers of the genitalia, and ocular inflammation and were classified as suffering from the ocular type of Behçet's disease. All have been followed up regularly with at least three follow-up visits per year.

TREATMENT

Corticosteroid drops (dexamethasone 0·1%, prednisolone 1·0%, fluometholone 0·1%) were instilled four to eight times daily according to the severity of the ocular reaction and mydriatics-cycloplegics (atropine 1%, scopolamine 0·25%, neosynephrine 10%, cyclopentholate 1%) if the anterior segment was affected. Subconjunctival or subtenon slow-release steroid preparations (Depo-Medrol (methylprednisolone acetate) 20 mg) were injected if the initial response to drops was not satisfactory. Systemic treatment was started only if the patient presented with marked posterior segment involvement and/or prominent anterior segment inflammatory activity that did not respond to local therapy in one or both eyes. Initially all patients were treated with steroids, receiving oral prednisone 1 to 2 mg/kg/day for four days, with a gradual decrease of the dose in accordance with the clinical signs. When the ocular inflammatory reactions were not controlled by a dose less than 35 mg/day (approximately 0·5 mg/kg/day) and exacerbations were observed under this regimen, the steroids were gradually stopped and the patients treated with the second line of drugs.

As second line the patients received during this period any of the following: colchicine (18 patients) with an initial dose of 0·05 mg/kg/day and gradual reduction to a maintenance dose of 0·5 mg daily within one month; chlorambucil (20 patients) in doses of 0·1 to 0·2 mg/kg/day as a starting dose, titration according to the inflammatory and haematological response, and a final maintenance dose of 2 mg/day; azathioprine (four patients) in doses of 2 mg/kg/day and a maintenance dose of 75 to 100 mg/day. Two of the patients treated with chlorambucil underwent plasmapheresis because of frequent relapses. Two of the patients treated initially with colchicine were later tried on levamisole 50 mg orally thrice daily.

Results

Of the 49 patients with the ocular type of Behçet's disease 42 were born in countries of the Mediterranean basin, five in Iran, and two in Iraq (Table 1). Of the 12 patients born in Israel the parents' origin was in countries of the Mediterranean basin in 10 cases, from Russia in one case, and from Poland in one case. Thirty-six patients were male (73%) and 13 were female (27%).

The ophthalmic manifestations observed in the 49 patients encompassed both the anterior and posterior segments and reflected the vasculitis of the ocular blood vessels. Careful examination of the peripheral fundus disclosed choroidal and/or retinal exudates, with sheathing of the blood vessels in all cases. In three of the cases the findings in the peripheral fundus were the earlier ocular manifestations with anterior uveitic signs appearing at a later stage of the disease. Hypopyon was recorded in 17 out of the 49 patients at different stages and was observed more than once in seven cases. In 13 patients hypopyon was a late phenomenon appearing during exacerbation periods. In four eyes of four patients hypopyon was an early event. In three of these patients hypopyon was the presenting ocular manifestation leading to the diagnosis of Behçet's disease. None of our patients showed any involvement of the cornea and/or sclera during the period of follow-up.

Table 1 *Countries of birth of patients with the ocular type of Behçet's disease*

Country	*Number of patients*
Jordan	16
Israel	12*
North Africa	11
Iran	5
Greece	2
Iraq	2
Turkey	1
Total	49

* Of the 12 patients born in Israel the parents of 10 originated from countries of the Mediterranean basin. In one case the parents originated from Russia and the other from Poland.

All patients initially responded favourably to high doses of corticosteroids with a marked decrease in ocular inflammatory signs and improvement of visual acuity. However, most of the patients had relapses and exacerbations of the inflammatory signs on lowering of the daily steroid dose. Forty-two of the patients were subsequently treated with chlorambucil (20 patients), colchicine (18 patients), and azathioprine (four patients), while seven patients continued to be treated with high doses of steroids. As illustrated in Table 2, all seven patients under maintained high doses of steroids responded to the treatment and had a remission period ranging from three to 14 months with an average of eight months. Treatment with chlorambucil induced remission of the ocular inflammatory processes in 16 out of 20 patients. In four patients no benefit was observed. While the average period of remission for the whole

Table 2 *Modes of treatment* modalities for the 49 patients*

Treatment	*Number of patients*		*Period of remission (months)*	
	Total	*Responders*	*Average*	*Range*
Steroids	7	7	8	3–14
Chlorambucil	20	16	6	0–25
Colchicine	18	8	3	0–7
Azathioprine	4	1	2	0–8
Plasmapheresis†	2	1	2	0–4
Levamisole‡	2	1	2	0–4

* All patients were initially treated with steroids and switched to another treatment after resistance to steroids developed. The seven cases that remained under steroids received increased doses and were not given a trial of immunosuppressive drugs because of secondary considerations.

† Two of the patients who were treated with chlorambucil and relapsed subsequently underwent plasmapheresis.

‡ Two of the patients who were treated with colchicine and relapsed were treated with levamisole.

group treated with chlorambucil was approximately six months, two of the responding patients had no relapses for 24 and 25 months in each case. The response to colchicine or azathioprine was less obvious. Eight of 18 patients responded favourably to colchicine with a relatively short period without exacerbations, while only one patient out of four treated with azathioprine showed a significant decrease of the inflammatory signs. After failure of the cytotoxic immunosuppressive drugs, patients were again treated with high doses of steroids, with variable degree of responses. Two patients also underwent plasmapheresis and two were treated with levamisole without success (Table 2).

Secondary complications were observed in almost all eyes. These included early events such as lenticular changes, posterior synechiae, secondary glaucoma, vitreous opacities and organisation, and macular oedema. Later complications included iris and retinal neovascularisation, traction retinal detachment, vascular insufficiency, and optic atrophy. While the early secondary complications were relatively amenable to treatment and/or control, the late complications were uncontrollable and were the cause of the poor vision or intractable blindness.

Table 3 illustrates the deterioration in visual acuity that occurred during the period of follow-up. Of the 49 patients (98 eyes) observed during three years or less after initiation of the ocular manifestations 51 retained excellent visual acuity and only two eyes showed total loss of vision. Thirty-nine patients (78 eyes) were followed for up to six years. Of these, 25% had finger counting at a distance of 1 metre to distinction of hand movements in front of their eyes or lost vision totally. Among the 26 patients (52 eyes) followed for up to 10 years five eyes retained a good visual acuity of 6/6 to 6/12, while 30% of the eyes lost vision totally, 26% had only finger counting to hand movements, and an additional 18% had visual acuity within the range of legal blindness.

Table 3 *Residual visual acuity during follow-up*

Visual acuity	*Years of follow-up*					
	≤3		*>3–6*		*>6–10*	
	*No.**	*%*	*No.*	*%*	*No.*	*%*
6/6–6/12	51	52	22	28	5	10
6/15–6/30	30	31	20	26	8	16
6/60–6/120	9	9	13	17	9	18
FC–HM	6	6	18	23	14	26
NLP	2	2	5	6	16	30
Total	98	100	78	100	52	100

* No.=Number of eyes in each group, with % of total.
FC=finger counting at a distance of 1 to 3 m.
HM=perception of hand movements.
NLP=no light perception (generally these eyes were phthisic).

Discussion

Deeper knowledge of the possible affection of various organs and the emergence of complex diagnostic criteria with subtype divisions to 'complete;' 'incomplete,'[12] and even 'suspected' types of Behçet's disease led to disparate reports on the incidence of involvement of the various organs in this disease.[10-15] It appears that these large discrepancies along with the optimistic or pessimistic outcome of the various modes of treatment have largely depended on the specialty of the reporter(s) and his subjective evaluations, biased in most cases by insufficient follow-up data.[16-18] Although Behçet's is undoubtedly a multisystem disease, the ocular inflammatory signs and the high incidence of loss of visual acuity are its most dramatic effects. Because on the one hand of the prominence of the ocular manifestations and on the other our earlier clinical impressions of the possible difficulty of differential diagnosis from other collagen disease in the absence of ocular involvement, it has been our practice during the last decade to divide Behçet's disease into 'ocular' and 'non-ocular' types. Based on similar observations, a subdivision into mucocutaneous and neuro-ocular types of Behçet's has been suggested.[19] Forty-nine patients fulfilled the criteria for the ocular type of Behçet's disease and were followed up regularly for up to 10 years in our clinic. This unique group enabled us to assess the rate of visual deterioration in this disease. We have observed that only 2% of the eyes lost total vision within the first three years after initiation of the ocular symptoms, while within 10 years 30% lost vision totally, 26% remained with finger counting or perception of hand movements in front of their eyes, and an additional 18% were within visual acuity of legal blindness. Therefore in our group of patients, regardless of the type of treatment, 74% of the eyes lost useful vision six to 10 years after initial diagnosis.

The ophthalmic manifestations of Behçet's disease are the reflection of the uveitis and retinal vasculitis. These manifestations involve both the anterior and posterior segments within two years of the recording of initial symptoms regardless of whether the initial symptoms were an iridocyclitis with or without hypopyon or a vasculitis of the vessels in the fundus periphery. Apart from the recurrent sterile hypopyon (when present) and the pipe stem sheathing of the retinal blood vessels at a later stage of the disease, no other ocular affections or secondary complications are specific to Behçet's disease. However, in our opinion the lack of corneal or scleral involvement is characteristic. Therefore, when keratitis and/or episcleritis are observed, as in some reports,[20] possible secondary phenomena and/or a differential diagnosis from other collagen diseases has to be considered.

Reliable figures regarding the natural history of visual deterioration in Behçet's disease are not available, while the prognostic effect of the various modes of treatment on the visual outcome is not clear. It is our clinical impression that the frequency of the attacks of ocular inflammatory exacerbation and their length are diminished by treatment with large doses of corticosteroids and/or immunosuppressive drugs. However, as observed during this study, the long-term prognosis for vision remains very poor. High doses of steroids can control the inflammatory processes and a unanimous response to the steroids is observed initially. However, a state of resistance to the steroid treatment develops, followed by an increase in the severity and number of exacerbations. The effect of cytotoxic-immunosuppressive drugs on the ocular manifestations of Behçet's disease has been variable. Chlorambucil was clearly beneficial in 75% of the patients. Colchicine was less effective and reduced temporarily the ocular inflammatory signs in only 45% of the cases, while the response to azathioprine was negligible. Although only 16 out of 20 patients responded favourably to treatment with chlorambucil, two of these were in remission for 24 and 25 months, the longest period without inflammatory activity we have observed so far in Behçet's disease. These results, although not fully compatible with the outstanding benefits reported by others using chlorambucil,[21,22] may explain the enthusiasm for this drug. It is undeniable that both the large doses of steroids and to a greater extent the long-term use of chlorambucil are not without harm and may have deleterious outcomes.[20,23,24] These have to be considered against the threat of blindness when deciding about the type of treatment in Behçet's disease.

Recently the influence of cyclosporin A (CsA) on the acute exacerbations of Behçet's disease has been tested with some encouraging results.[25-27] However, owing to the chronicity of the disease process and the unpredictability of remissions and exacerbations of the inflammatory reactions, there is a need for masked evaluations, longer follow-up data, and larger numbers of patients for adequate and unbiased testing of this novel drug. Such studies are now in progress and will hopefully provide the needed information in the future.

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Haemorrhage in the lens: spontaneous occurrence in congenital cataract

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SUMMARY A 2-month-old female infant had bilateral congenital cataract. In the left eye a blood clot was situated on the subcapsular polar cataract. An uneventful lensectomy combined with anterior vitrectomy by the pars plicata approach revealed remnants of the posterior portion of hyaloid artery on the optic nerve head. It is likely that the spontaneous and long-lasting haemorrhage in the lens had been caused by rupture of the anterior end of the hyaloid artery attached to the posterior lens surface and had occurred in the late prenatal or early postnatal period.

Haemorrhage in the crystalline lens is very uncommon.[1] Occasional cases have been caused by rupture of the lens capsule allowing the blood to enter the lens stroma, as complications of intraocular surgery,[2] or from perforating ocular injury.[3] We report the case of a 2-month-old patient who had a spontaneous and long-lasting haemorrhage in the lens associated with congenital posterior polar cataract.

Case report

A female infant was born with birth weight of 3840 g after a full-term, normal, spontaneous delivery. The mother had a history of rubella infection at the age of 12 years and had no problems during the pregnancy. There was no contributory family history or parental consanguinity. Two weeks after the birth the mother had noticed a whitish appearance in the infant's pupils. At the age of 2 months the infant was referred to us for investigations of bilateral congenital cataract.

Physical examinations revealed that the infant had developed well and had no systemic anomalies. Radiological examinations, including skull CT scan, showed normal appearances. The results of the following laboratory studies were also normal: erythrocyte count, packed cell volume, leucocyte count, platelet count, bleeding and coagulation time of the blood, serological tests for viral infections, chromosomal analysis of the leucocyte.

On ocular examination the infant was found to have poor fixation on objects. There was no abnormality in the ocular adnexas and outer segments. The corneas were clear and measured 8·5 mm in diameter. The anterior chambers were clear and normally deep, with well developed angle structures. The pupils were round and reacted well to light or mydriatics. The lenses had prominent opacities, which were judged to inhibit visual development. They were treated surgically as described below. Applanation tonometry gave 10 mmHg in both eyes. The electroretinograms, ocular ultrasonograms, and orbital CT scans gave normal results.

RIGHT EYE

The lens was normal in position, shape, and size. The anterior portion of the lens was clear, but there was a dense, circular opacity in the subcapsular cortex of the posterior pole. There was neither haemorrhage nor aberrant vessel in the lens. The vitreous underlying the posterior polar cataract was invisible. The peripheral region of the vitreous and fundus visible through the clear peripheral lens was normal.

Because the infant's fixation remained poor, an aspiration of the lens material by the limbal approach was performed on the 130th day of life. Although most of the lens could be easily aspirated, the dense posterior polar opacity was so calcareous and firmly adherent to the posterior lens capsule that it had to be left, and it was later dissected during cataract surgery of the fellow eye. As a result, the pupillary area became clear, and ophthalmoscopy revealed normal vitreous and fundus.

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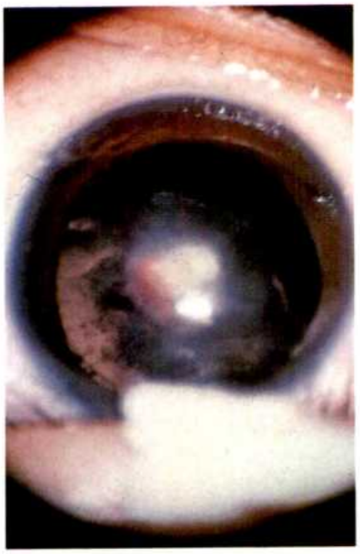

Fig. 1 *Deposit of clotted blood on the posterior polar cataract.*

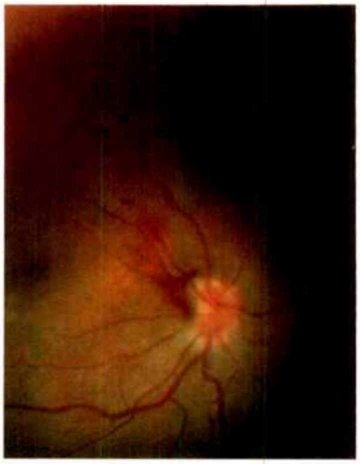

Fig. 2 *Postoperative haemorrhage on the optic nerve head projecting into the vitreous cavity from the persistent hyaloid artery.*

LEFT EYE

Several thread-like remnants of pupillary membrane were attached to the iris only. The lens was normal in position, shape, and size. There was a circular dense opacity, situated in the subcapsular cortical region of the posterior pole and surrounded by a larger but weaker opacity. On the anterior surface of the temporal border of the central dense opacity was deposited a rectangular, sharply-delimited haemorrhage, about 2 × 1 mm, which appeared clotted and must have persisted for a long time. No vascular components were detectable adjacent to the haemorrhage. Because of this dense opacity the lens capsule in the posterior pole and the underlying vitreous could not be examined (Fig. 1). The whole anterior cortex, embryonal nucleus, and peripheral portion of the posterior cortex were clear, permitting us to visualise normal peripheral vitreous and fundus.

During observations over two months after the initial visit the clotted haemorrhage in the lens remained unchanged. Lensectomy combined with a shallow anterior vitrectomy was carried out on the 165th day of life by the pars plicata approach: the clotted haemorrhage was easily aspirated together with the neighbouring lens materials. A part of the calcareous cataract adhered to the posterior lens capsule was excised and aspirated en bloc with the anterior vitreous; no bleeding occurred, nor were any aberrant vascular or fibrous tissues present. Light microscopic examinations of aspirated materials revealed lens capsule, lens epithelium, and normal and degenerated lens fibres intermingled with clotted blood, but no vascular or fibrous tissues.

The postoperative course was uneventful, and the pupillary area became clear enough for us to examine the vitreous and fundus. On the second postoperative day ophthalmoscopy revealed linear fresh haemorrhages on the optic nerve head, projecting a short distance into the vitreous cavity, and on the neighbouring retina (Fig. 2). These haemorrhages cleared completely in three weeks and were followed by retention of a fine strand devoid of blood originating from the surface of the optic disc. Eventually the infant learned a stable, good central fixation by wearing aphakic correction glasses.

Discussion

Haemorrhage in the lens as a solitary condition is very rare. Previous reports described cases in which the haemorrhage in the lens occurred as complications of intraocular surgery, such as a filtration operation or peripheral iridectomy for glaucoma,[2] or as sequelae of perforating ocular injury.[3] These complications must have been caused by rupture of the lens capsule, in particular a part of the anterior capsule, allowing blood from the anterior chamber to enter the lens stroma.

It is noticeable that the infant reported on here had an apparently spontaneous haemorrhage in the lens in the sense that it was not subject to either surgical or traumatic intervention. Stein[4] briefly reported a similar case: a 4-year-old child with unilateral congenital cataract and convergent strabismus had small haemorrhage under the posterior lens capsule, which remained unchanged for a year.

A common clinical feature in these two cases of spontaneous haemorrhage in the lens is a deposit of clotted blood in the congenital posterior polar cataract. In addition to the brief note by Stein[4] the present case may offer some clues for understanding the pathogenesis of the haemorrhage in the lens. The right eye had neither haemorrhage in the lens nor overt ocular anomaly. By contrast the left eye, with its haemorrhage in the lens, had remnants of pupillary membrane and, moreover, persistent posterior end of hyaloid artery on the optic disc projecting a short distance into the vitreous cavity. These observations indicate an overall delay of regression of the fetal vascular systems round the lens and vitreous,[5] and they also suggest that the anterior end of the hyaloid artery is persistent. It may therefore be possible to assume that a rupture of the anterior end of the hyaloid artery attached to the posterior lens surface caused bleeding into the lens. The incident must have occurred in the late prenatal period, or in the early postnatal period, since the haemorrhage in the lens was clotted, and the anterior end of the hyaloid artery had regressed two months after birth.

Haemorrhage in the lens must remain for a long time. For the management of a congenital cataract associated with it the pars plicata approach for lensectomy combined with anterior vitrectomy may be better than the conventional corneal approach, since firm adherence of the posterior lens capsule to the anterior vitreous membrane is to be expected. In the present case fresh haemorrhages from the persistent hyaloid artery occurred on the optic disc in the early postoperative days. A similar complication may also occur spontaneously.[6]

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Intravenous lignocaine pretreatment to prevent intraocular pressure rise following suxamethonium and tracheal intubation

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SUMMARY Intravenous lignocaine (1·5 mg kg^{-1}) was evaluated in patients undergoing intraocular surgery as a means of preventing the rise in intraocular pressure which accompanies tracheal intubation. In patients given either suxamethonium or pancuronium to facilitate tracheal intubation, lignocaine pretreatment conferred no benefit over placebo in preventing the intraocular hypertensive response.

Laryngoscopy and tracheal intubation induce potent cardiovascular pressor responses which may cause myocardial ischaemia and cardiac arrhythmias in susceptible patients.[1] They also cause a significant increase in intracranial[2] and intraocular pressures,[3] which may have serious consequences in certain patients.

Intravenous lignocaine has been used with some success in attenuating these responses. Hamill *et al.*[4] found that intravenous lignocaine (1·5 mg kg^{-1}) reduced but did not completely abolish the haemodynamic effects of laryngoscopy and intubation. Donegan and Bedford[2] found that intracranial pressure (ICP) fell following intravenous lignocaine and that the rise in ICP accompanying tracheal suctioning was also attenuated. Poulton and James[5] found that intravenous lignocaine in a dosage of 1·5 mg kg^{-1} could significantly suppress the cough reflex.

Little work has been done in assessing intravenous lignocaine for prevention of intraocular hypertension. A recent review of the effects of anaesthesia on intraocular pressure[6] showed that no presently used method of preventing suxamethonium-induced intraocular hypertension was completely effective. In view of the success of intravenous lignocaine in attenuating the haemodynamic responses and ICP rise accompanying tracheal intubation it seemed worthwhile to assess its efficacy in preventing the rise in intraocular pressure which also accompanies this manoeuvre.

The aim of the present study was to evaluate the effect of lignocaine pretreatment on suxamethonium induced intraocular hypertension and its effect on intraocular pressure changes following tracheal intubation.

Patients and methods

Adult patients giving informed consent and undergoing cataract surgery under general anaesthesia were included prospectively into the study. Premedication was with oral diazepam 10 mg, given 90 minutes prior to surgery.

The patients were grouped by random number sequence into those who received suxamethonium (1·5 mg kg^{-1}) and those who received pancuronium (0·1 mg kg^{-1}) for muscle relaxation and subgrouped into those who received intravenous lignocaine (1·5 mg kg^{-1}) pretreatment and those who received placebo.

The anaesthesia sequence for patients given suxamethonium involved administration of lignocaine or placebo followed one minute later by thiopentone (4–5 mg kg^{-1}) and then suxamethonium (1·5 mg kg^{-1}) one minute after completion of thiopentone injection. Tracheal intubation was performed one minute after suxamethonium injection. In these patients intraocular pressure was measured just before suxamethonium administration, just before laryngoscopy, and one minute after tracheal intubation.

The anaesthesia sequence for patients given pancuronium involved administration of lignocaine or placebo followed one minute later by thiopentone

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(4–5 mg kg^{-1}) and pancuronium. As spontaneous breathing ceased, ventilation was controlled to maintain normocapnia (Siemens Elma 130 Infrarèd CO_2 Monitor) with 70% nitrous oxide in oxygen via face mask. Five minutes later tracheal intubation was performed. In these patients intraocular pressure was measured just before laryngoscopy and one minute after tracheal intubation.

After the last measurement was made a volatile anaesthetic agent was introduced to maintain anaesthesia, and ventilation was controlled in all cases. Pancuronium was given if necessary to the patients who had been given suxamethonium only after this time. No patient received opiates or beta blockers, and local anaesthetic spray to the larynx was not used.

Measurements of intraocular pressure were made in the eye not undergoing surgery with a Digilab 30RT Pneuma-Tonometer/Tonographer, which was calibrated before and rechecked after each set of measurements. This instrument, designed exclusively for intraocular pressure measurement and using a pneumatic sensor, operates on the principle of applanation tonometry and records intraocular pressure continuously in mmHg, using a freely moving pen recorder and calibrated paper strip. Values for intraocular pressure for all groups were compared by Student's *t* tests.

At the same time as intraocular pressure measurements were performed arterial blood pressure and heart rate were measured with a Vita-Stat 901-S blood pressure monitor.

Results

A total of 40 patients were studied, 10 in each subgroup. No significant differences between the subgroups were seen with regard to age, sex, and weight (Table 1).

In the suxamethonium subgroups the change in IOP (mean 0·35 mmHg±2·68 SD), following suxamethonium administration failed to reach statistical significance. However, in these subgroups the IOP was significantly increased (mean 4·05 mmHg±3·145 SD, $p<0{\cdot}001$) following tracheal intubation (Table 2).

In the pancuronium subgroups a similar significant increase in IOP followed tracheal intubation (mean 5·4 mmHg±4·67 SD, $p<0{\cdot}001$). The systemic arterial pressure and heart rate increased in parallel with the IOP in all cases (Table 3).

In both the suxamethonium subgroups and the

Table 1 *Demographic data for patient subgroups (mean±standard deviation)*

	Suxamethonium subgroups		*Pancuronium subgroups*	
	Placebo	*Lignocaine*	*Placebo*	*Lignocaine*
Age	72·8±11·8	70·8±10·7	73·7±6·3	66·2±10·7
Sex M:F	3:7	2:8	4:6	2:8
Weight	61·2±5·2	59·0±8·0	62·9±10·5	67·9±12·7

Table 2 *Intraocular pressure (mmHg), blood pressure (mmHg), and heart rate (/min) with and without lignocaine pretreatment. Mean (standard deviation)*

	Presuxamethonium		*Preintubation*		*Postintubation*	
	Placebo	*Lignocaine*	*Placebo*	*Lignocaine*	*Placebo*	*Lignocaine*
Intraocular pressure	16·2 (5·0)	19·1 (5·4)	16·9 (4·7)	19·1 (4·1)	21·1 (3·8)	23·1 (5·9)
Systolic arterial pressure	134·8 (14·7)	135·0 (17·9)	143·0 (19·0)	135·2 (15·6)	158·5 (16·3)	149·1 (23·9)
Heart rate	79·6 (8·8)	80·9 (9·4)	82·0 (10·7)	81·0 (10·8)	84·4 (10·5)	84·5 (15·5)

Table 3 *Intraocular pressure (mmHg), arterial pressure (mmHg), and heart rate (/min) with and without lignocaine pretreatment. Mean (standard deviation)*

	Preintubation		*Postintubation*	
	Placebo	*Lignocaine*	*Placebo*	*Lignocaine*
Intraocular pressure	18·7 (7·9)	14·8 (3·5)	22·3 (5·3)	22·0 (4·3)
Systolic arterial pressure	131·5 (27)	146·8 (18·3)	151·3 (32·0)	158·0 (14·8)
Heart rate	86·0 (22·9)	81·5 (16·9)	87·6 (19·3)	94·9 (20)

pancuronium subgroups lignocaine pretreatment failed to have any effect on the rise in IOP accompanying tracheal intubation ($p>0{\cdot}05$).

Discussion

With improved anaesthetic agents and techniques, general anaesthesia is used increasingly in ophthalmic surgery in an attempt to optimise conditions for intraocular surgery. Controlled hyperventilation significantly reduces intraocular pressure (IOP) but is preceded by a significant rise in IOP due to tracheal intubation. In most patients intraocular hypertension following tracheal intubation is of short duration and is inconsequential. In patients undergoing cataract surgery the IOP is likely to have returned to normal owing to controlled hyperventilation before the eye is opened. In patients with perforating eye injuries, however, any rise in intraocular pressure irrespective of duration may be hazardous, as it may precipitate extrusion of intraocular contents and may further endanger sight in that eye. For this reason also the administration of suxamethonium to patients with perforating eye injuries is controversial, since it is known to increase intraocular pressure.

Many drugs have been used in an attempt to obtund the undesirable effects of suxamethonium and tracheal intubation, including small doses of non-depolarising neuromuscular blocking drugs,[7,8] 'self-taming' with small doses of suxamethonium[8] and with preinduction doses of intravenous diazepam,[9] hexafluorenium,[10] and acetazolamide.[11] No method of pretreatment has been found to be completely satisfactory.[6] A review of the literature showed that, though intravenous lignocaine pretreatment has been the subject of a number of studies, only one evaluated its effect on intraocular pressure. Smith *et al.*[3] used 1 or 2 mg kg^{-1} of intravenous lignocaine and found it to be 'ineffective in preventing the rise in intraocular pressure following succinylcholine and/or tracheal intubation.'

In the present study, lignocaine pretreatment was not found to have any effect on IOP following suxamethonium. It may be inferred that this would also be the case in patients with perforating eye injuries.

It is a reasonable criticism of this study that tracheal intubation was performed under light (thiopentone) anaesthesia and that resultant haemodynamic responses may have contributed to the changes in IOP observed. Since this technique is likely to compare with that used to anaesthetise a patient with a post-traumatic eye injury, however, this is most likely to compare with relevant conditions.

Of greater significance was the fact that changes in IOP following suxamethonium were unimportant compared with the major changes in IOP that occurred with tracheal intubation. Much has been written about the potentially hazardous use of suxamethonium but little about the dangers of responses to intubation in patients with eye injuries. It would seem from the present study that the rise in IOP from tracheal intubation is of such magnitude as to render the suxamethonium effect unimportant. The aim of future studies in our opinion should be directed at inhibiting responses to intubation rather than suxamethonium. Clearly intravenous lignocaine pretreatment is not the answer.

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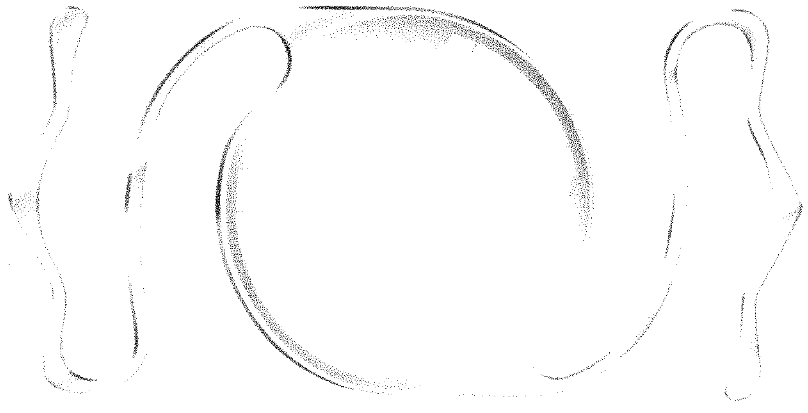

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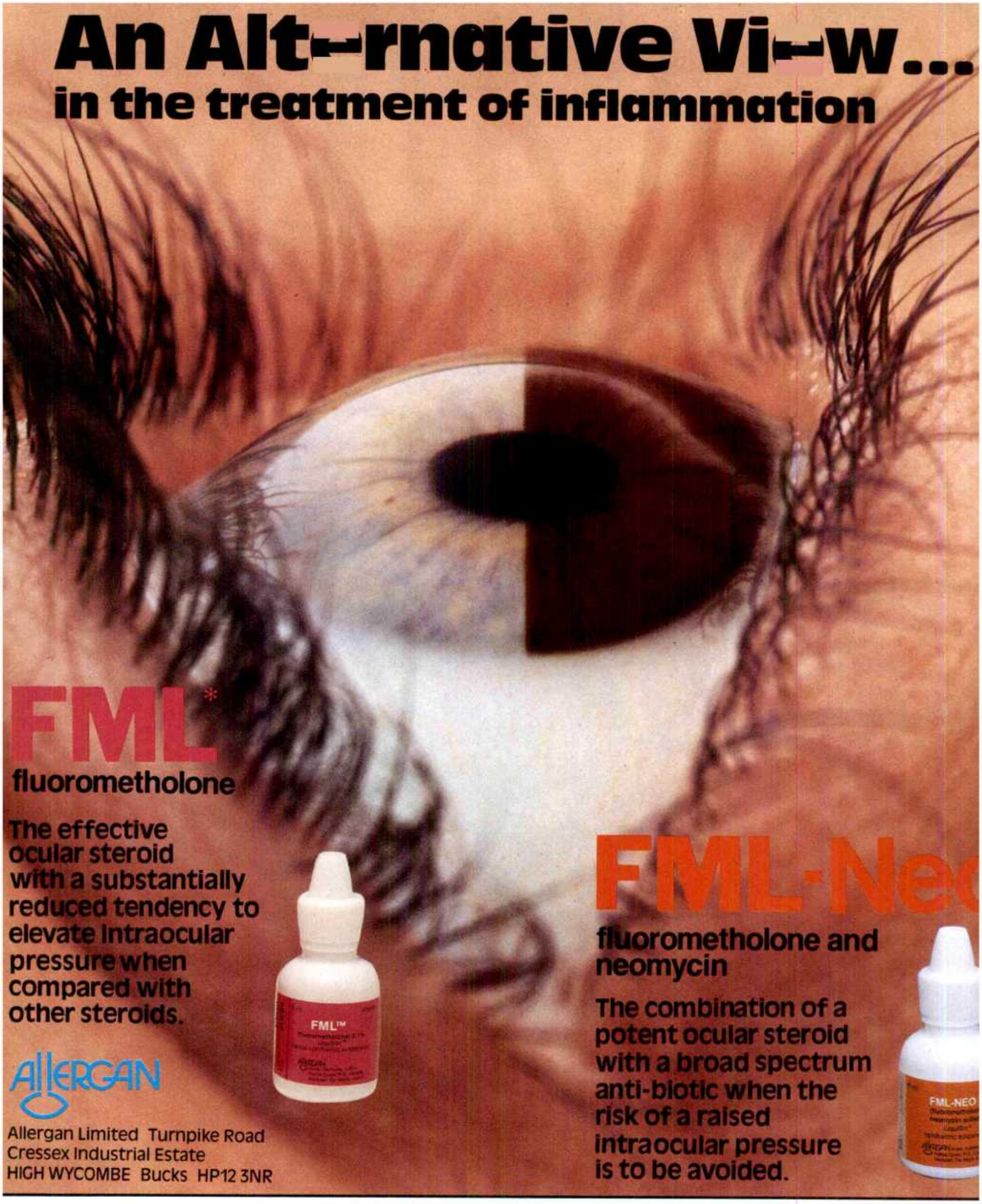

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British Journal of Ophthalmology, 1986, **70**, 599–602

Association between optic disc haemorrhages in glaucoma and abnormal glucose tolerance

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SUMMARY Data concerning the results of glucose tolerance tests and levels of intraocular pressure were analysed for 120 patients with primary open-angle glaucoma, many of whom had been under observation for a period of four to five years. The patients consisted of two groups: in 62 patients a disc haemorrhage had been recorded at some time during the observation period, and in 58 no haemorrhages had been seen. Patients with disc haemorrhages had a higher incidence of abnormal glucose tolerance or frank diabetes and lower intraocular pressures than those without haemorrhages.

Evidence of an association between diabetes mellitus and glaucoma has existed for more than 20 years, and in 1971 Becker[1] presented a review of previous work combined with his own investigations from which he drew the clinical implications that glaucoma should be suspected in diabetics, and that diabetes should be suspected in patients with primary open-angle glaucoma, especially those with low tension glaucoma. The present investigation was undertaken to examine the association between glaucoma and diabetes with particular reference to the occurrence of haemorrhages on the optic disc.

It has recently been pointed out[2] that Bjerrum described haemorrhages on the optic disc in glaucoma almost 100 years ago, but thereafter little attention seems to have been paid to this observation until Drance and Begg[3] published their description. It has now been established that disc haemorrhages occur in at least one-third of patients with open-angle glacoma,[4,5] that they may be observed in the early stages of the disease,[6] and that they are related to the progression of visual field loss.[7] Although the precise relationship of these haemorrhages to the pathology of the glaucomatous optic nerve head is still not clear, it was considered that our present knowledge of changes in small blood vessels in diabetes mellitus indicated a need to make a special retrospective study of a possible association between abnormal glucose tolerance and glaucomatous disc haemorrhages. Some subsidiary observations were made of systemic blood pressure and of the location of disc haemorrhages.

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Patients and methods

The investigation involved two groups of patients with established primary open-angle glaucoma, manifested by glaucomatous cupping of the optic disc and characteristic field defects. The first group consisted of 62 patients in whom a disc haemorrhage had been observed at some time during routine follow-up. The second group consisted of 58 patients who were examined at approximately the same time as those in the first group but in whom a disc haemorrhage had never been observed. They were selected from the general run of glaucoma follow-up patients only in so far as an attempt was made to make the groups comparable as regards age and sex composition. Most of the patients had been seen in the glaucoma clinic at intervals of 3–6 months for an average period of 4–5 years. All patients had had complete ocular examinations, including examinations of visual acuity, intraocular pressure, visual fields, and fundus, together with disc photography, measurement of systemic blood pressure, and recording of pulse rate. In addition they all had random blood sugar estimations and those who had random blood sugar levels greater than 5 mmol/l were subjected to a standard glucose tolerance test. This involved fasting from midnight and stopping all medication for 48 hours, but without restriction of water, until arrival in the clinic on the following morning. At this time the visual acuity, intraocular pressure, systemic blood pressure, and pulse rate were recorded, and a sample of venous blood was collected. Patients were then given 75 g of glucose dissolved in 200 ml of water flavoured with lemon or orange to drink over a short period of time. A sample of blood at 30-minute intervals was collected over two hours. All blood samples were sent to the Pathology Department of the Institute of Ophthalmology for estimation of plasma glucose levels. The intraocular pressure, blood pressure, and pulse rate were also recorded at 30-minute intervals during the test.

Results

Table 1 shows that there was no significant difference between the two groups of patients as regards age and sex distribution. Table 2 shows maximum pretreatment intraocular pressures recorded at any stage, random blood sugar levels, and systemic blood pressures in the two groups. There was no significant difference between the groups as regards systemic blood pressure, but 15 patients with disc haemorrhages and six without had diastolic pressures of 110 mmHg or above.

There were significant differences between the two groups as regards random blood sugar levels and maximum recorded intraocular pressures. These results are shown graphically in Fig. 1, from which it can be seen that patients with disc haemorrhages tended to have higer blood sugar levels and lower intraocular pressures than those without haemorrhages ($p<0\cdot05$).

The results of glucose tolerance tests (GTT) are shown in Table 3. The GTT results have been divided as normal, impaired, or diabetic, according to the criteria laid down by the World Health Organisation Expert Committee on Diabetes Mellitus.[8] The higher incidence of impaired and diabetic GTT results in patients with disc haemorrhages was significant (χ^2= 8·8, $p<0\cdot01$). These results are presented in greater detail in Fig. 2.

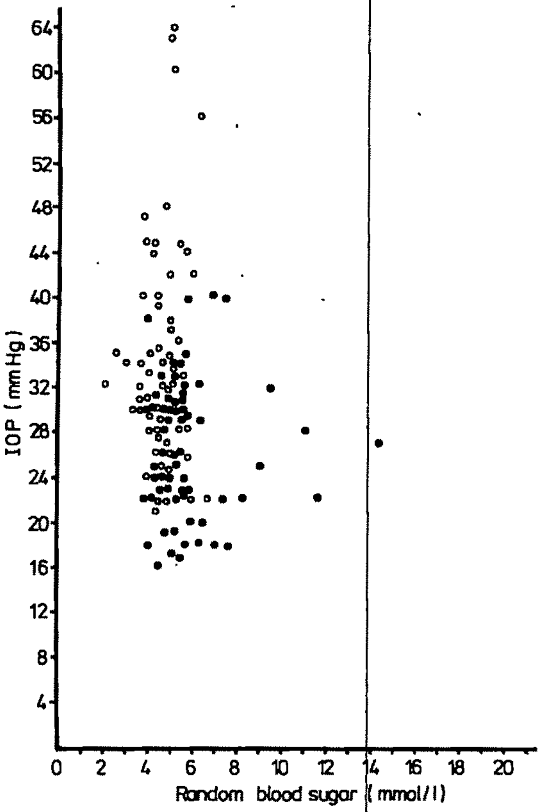

Fig. 1 *Random blood sugar levels and maximum recorded intraocular pressures in the two groups of patients.* ○=*Without disc haemorrhage.* ●=*With disc haemorrhage.*

Table 1 *Age and sex distribution of patients*

Patients	*No.*	*Male*	*Female*	*Age, mean± SD (range)*
With disc haemorrhage	62	28	34	68·4±20·9 (44–88)
Without disc haemorrhage	58	28	30	67·8±20·86 (51–38)

The topographical distribution of the observed disc haemorrhages is shown in Fig. 3, indicating that 50% of haemorrhages occurred in the lower half of the disc between 5 and 7 o'clock, especially in the inferotemporal region. The mean maximum recorded intraocular pressure in patients showing haemor-

Table 2 *IOP, blood glucose, and systemic BP in the two groups of patients*

Patients	*No.*	*Maximum IOP, mean±SD (mmHg)*	*Random blood glucose, mean±SD (mmol/l)*	*Blood pressure, mean±SD (mmHg)*	
				Diastolic	*Systolic*
With disc haemorrhage	62	26·3±6·13	5·94±1·90	97±12·6	161±20·6
Without disc haemorrhage	58	34·7±10·51	4·69±0·79	94±11·4	159±18·6

Table 3 *Incidence of impaired glucose tolerance and diabetes in the two groups of patients*

Patients	*No.*	*Percentage with normal glucose tolerance*	*Percentage with impaired glucose tolerance*	*Percentage diabetic*
With disc haemorrhage	48	52·1	33·3	14·6
Without disc haemorrhage	32	84·4	9·4	6·3

rhages in the horizontal (that is, nasal and temporal) sectors of the disc was 29·88 mmHg (SD+12·46), as compared with 23·20 mmHg (SD=6·55) for patients with haemorrhages in the vertical (that is, upper and lower) sectors of the disc; this difference was significant (p=0·005).

Discussion

Our study has shown two differences between glaucoma patients with disc haemorrhages and those without. The first difference was that almost 50% of patients with haemorrhages had impaired glucose tolerance or frank diabetes as compared with about 15% of patients without haemorrhages, this difference being statistically significant. Previous workers have measured blood sugar levels two hours after a meal[9] or have measured fasting glucose levels or done glucose tolerance tests on a small number of patients[10] without finding any differences between patients with and without haemorrhages. The fact that our study showed that a difference may be due to the application of rather more stringent tests of glucose metabolism to a fairly large number of patients. The second difference which we found (Fig. 1) was that disc haemorrhages were detected more often in patients with lower intraocular pressures (IOP). It is to be borne in mind that the IOPs recorded here were the maximum (and therefore untreated) values recorded during the routine observation period of the patients. This observation is comparable with the finding of other workers[11] that

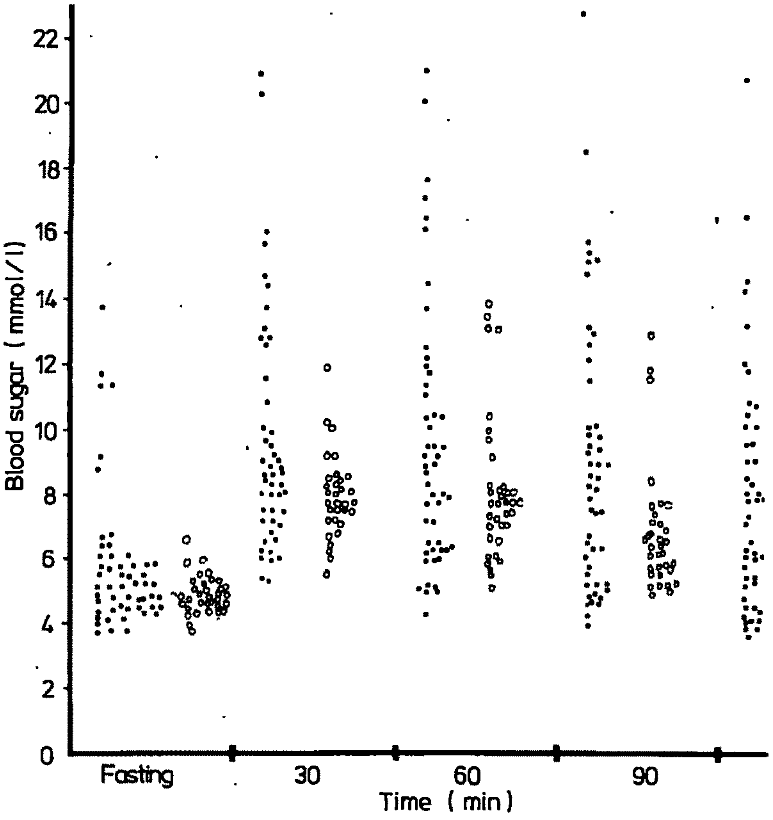

Fig. 2 *Glucose tolerance tests in the two groups of patients.* O= *Without disc haemorrhage.* ●= *With disc haemorrhage.*

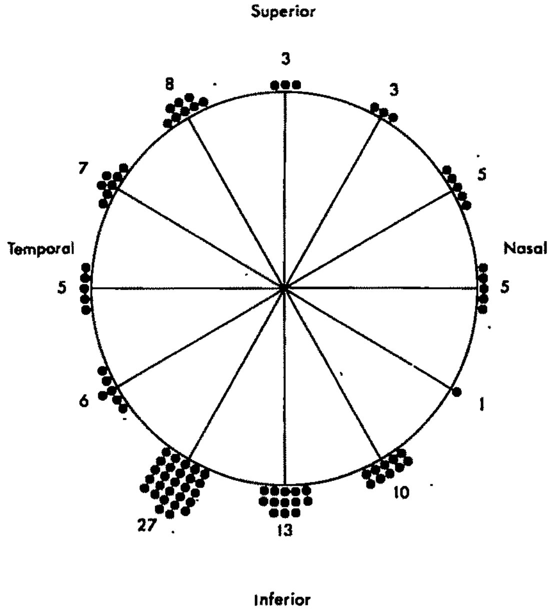

Fig. 3 *Distribution of haemorrhages in various sectors of the disc.*

disc haemorrhages are relatively common in low tension glaucoma.

By contrast no conclusions could be drawn from our study regarding the possible influence of the level of systemic blood pressure on the occurrence of disc haemorrhages in glaucoma. On the one hand there was no significant difference in mean blood pressure between the two groups of patients, while on the other hand there was a slightly higher incidence of systemic hypertension (defined as having diastolic pressure of 110 mmHg or more) in the group with disc haemorrhages. Other workers[9] have found a significantly higher prevalence of systemic hypertension in glaucoma patients with disc haemorrhages as compared with those without. The unequal distribution of haemorrhages in the various sectors of the optic disc, already described by other authors[12] was confirmed in this study together with the variation in levels of IOP associated with the occurrence of haemorrhages in the different sectors. These findings are probably explicable in terms of structural variations in the disc tissues from sector to sector.[13 14]

The association of disc haemorrhages in glaucoma with disordered glucose metabolism and with low intraocular pressure may be explained in several ways, but the results of this investigation do not favour any particular explanation. They do, however, make one point of direct clinical interest. This is that there is a possibility of coexisting diabetes mellitus in the glaucoma patient not only in cases of low tension glaucoma but also when disc haemorrhages are observed.

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Haemolytic glaucoma occurring in phakic eyes

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SUMMARY The occurrence of haemolytic glaucoma in phakic eyes due to ghost cells has not previously been reported. Three cases of haemolytic glaucoma occurring over two years after massive vitreous haemorrhage in patients with an intact lens iris diaphragm are described. In one case there was histological confirmation of the presence of ghost cells in the anterior chamber. The mechanism proposed for the passage of ghost cells to the anterior chamber is through a defect in the anterior hyaloid face, created as the vitreous liquefies and degenerates. The reported cases were satisfactorily treated by trabeculectomy with anterior chamber washout, which management has not previously been reported in haemolytic glaucoma.

The term haemolytic glaucoma was introduced by Fenton and Zimmerman[1] to describe a case of secondary open-angle glaucoma occurring in a phakic eye shortly after a vitreous haemorrhage. They believed that the condition was due to haemorrhagic debris and pigment-containing macrophages blocking the angle recess and the trabecular meshwork. Fenton and Hunter[2] and Hunter[3] described the condition again in two phakic eyes. Phelps and Watzke[4] later ascribed five cases to the same mechanism, three of their cases after vitreous haemorrhage in phakic eyes, one case followed vitreous haemorrhage in an aphakic eye, and one followed a traumatic anterior chamber haemorrhage. Jaffe[5] mentioned several cases which he considered followed vitreous haemorrhage after cataract extraction.

Campbell *et al.*[6] in a classic paper described two cases of haemolytic glaucoma occurring in aphakic eyes, and they established that the cells blocking the trabecular meshwork were in fact degenerate ghost cells—rigid spherical degenerate red blood cells containing Heinz bodies, which had previously been described in the eye by Fuchs.[7] They presumed that these cells entered the anterior chamber through a rent in the anterior hyaloid face. Campbell *et al.*[8] then described six more cases complicating vitrectomy, and Campbell and Essigmann[9] further described 19 patients with ghost cell glaucoma in aphakic eyes which were clinically of the same pattern, and the diagnosis was confirmed by examination of the aspirate in seven eyes. They considered that the classical haemolytic glaucoma due to macrophage and haemoglobin blockage of the angle must be very rare, and they had not encountered a case. Campbell[10] later described 14 cases of ghost cell glaucoma following trauma, all with forward passage of ghost cells into the anterior chamber via an opening in the anterior hyaloid face. Recently Summers *et al.*[11] reported a case of ghost cell glaucoma following vitreous haemorrhage following cataract extraction, where the ghost cells were confirmed by phase contrast microscopy.

There remains some doubt whether haemolytic glaucoma can occur after vitreous haemorrhage, in the absence of trauma, in an eye with a clinically intact lens iris diaphragm. The earlier cases described include five with vitreous haemorrhage and an intact lens iris diaphragm, though the presence of ghost cells was not established.

We describe three cases with a typical clinical picture of haemolytic ghost cell glaucoma and an intact lens iris diaphragm with histological proof of ghost cell glaucoma in one case.

Case reports

CASE 1

A 73-year-old white female suffered a spontaneous right total vitreous haemorrhage on 11 March 1973 reducing her vision to perception of light, with a poor direct pupillary reaction to light and no fundus details

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visible. The left visual acuity corrected to 6/5, with a normal left fundus. Applanation tonometry was 12 mmHg in each eye. Her general health was said to be good, with neither diabetes nor hypertension.

Over the next two years the vitreous haemorrhage did not clear and she developed a right posterior subcapsular cataract. On 20 August 1976 she presented with right corneal oedema, a pressure of 42 mmHg, and brownish cells (2+) in the anterior chamber. This did not respond to pilocarpine 2% eyedrops. The anterior chamber depths were right 2·7 and left 2·6 mm, with no rubeosis iridis. On gonioscopy the right angle was open all around, with a raised ridge of light fawn coloured deposit overlying the posterior third of the trabecular meshwork, compared with only moderate pigment in the left angle. The right intraocular pressure rose to 70 mmHg in spite of intensive medical treatment.

On 12 January 1977 right trabeculectomy with anterior chamber washout was performed. Postoperatively the right intraocular pressure was low normal, but it then rose to 34 mmHg over the following month and was controlled to 19 mmHg by adrenaline 1% drops. Seven months after operation the vision was hand movements. By electronic tonography Po/C for the right eye was 616 and for the left eye 82. After two years the light fawn coloured layer on the trabecular mesh had disappeared, and the pressure was 12 mmHg on adrenaline 1% eyedrops.

Five years postoperatively the patient's health was failing, pressures were 16 mmHg in the right and 10 mmHg in the left eye on no treatment, and the vitreous haemorrhage could be seen to be clearing through a dense brown cataract.

CASE 2

A 58-year-old obese white female having poorly controlled hypertension presented on 3 May 1974 with a decreased vision in the left eye of 6/36 due to a haemorrhagic central retinal vein occlusion. The right corrected visual acuity was 6/5, but there was tortuosity of the veins of the right optic disc. The intraocular pressures were right 20 and left 17 mmHg. The vitreous haemorrhage did not clear.

On 27 April 1977 she presented with a blind painful left eye, though the pupil reacted directly to light. There was corneal oedema, with numerous brownish red cells in the anterior chamber and in the vitreous. The intraocular pressures were right 24 and left 75 mmHg, and the anterior chamber depths were right 3·1 and left 3·3 mm, with no rubeosis iridis and no view of the fundus through the dense vitreous haemorrhage. Gonioscopy showed that both angles were wide and open with a line of dark red blood cells along the posterior trabecular meshwork below. The diagnosis of haemolytic glaucoma was made, and she was treated with pilocarpine 2% eyedrops, prednisolone disodium phosphate 0·5% eyedrops, and oral acetazolamide, which controlled the intraocular pressure to 20 mmHg. Electronic tonography recordings were Po/C right 90, left 266.

Over the ensuing eight years the pressure remained controlled on timolol maleate 0·5% eyedrops, with some clearing of the vitreous blood and improvement of vision to hand movements. There is now a posterior subcapsular cataract and pseudoexfoliation of the lens capsule. There is a posterosuperior detachment of the degenerate syneretic vitreous.

CASE 3

A 42-year-old hypertensive white female gave a history of a right vitreous haemorrhage in 1971. It recurred two years later after a minor blow to the right side of her face, but there was no ocular evidence of contusion injury. The vision was right eye, counting fingers, left 6/6; the intraocular pressure was 14 mmHg in right and left eyes. A large right vitreous haemorrhage cleared in five months to reveal a superotemporal retinal vein occlusion with neovascularisation; this was treated with photocoagulation, the vision improving to 6/6.

On 17 December 1974 she suffered a further right vitreous haemorrhage, reducing her vision to counting fingers. It failed to clear in spite of further photocoagulation, remaining as a dense vitreous haemorrhage.

On 7 April 1978 she presented with a painful right eye. The right vision was perception of light, the left vision 6/5, and there was right corneal oedema. The pressure was not controlled by treatment and rose to 50 mmHg, with brownish cells in the anterior chamber, heterochromia iridis (right brown, left grey iris) and a 'hyphaema' which settled with a khaki layer above and a darker layer below (Fig. 1). It was not possible to see the right angle on gonioscopy while the left was wide and open.

A diagnosis of haemolytic glaucoma was made, and a trabeculectomy was carried out with washout of the anterior chamber and broad iridectomy. Histologically, after vital staining with methyl violet, the anterior chamber aspirate was reported to show 'great numbers of degenerate red blood cells or ghost cells as described by Campbell *et al*.[6] together with a small number of red blood cells and a very occasional leucocyte. The ghost cells contain Heinz bodies consisting of precipitated denatured haemoglobin attached to the cell membrane' (C H Greer). Sections of the trabecular meshwork showed 'ciliary muscle and the scleral spur together with the trabecular meshwork and Schlemm's canal, in both of which there are abundant normal appearing red blood cells

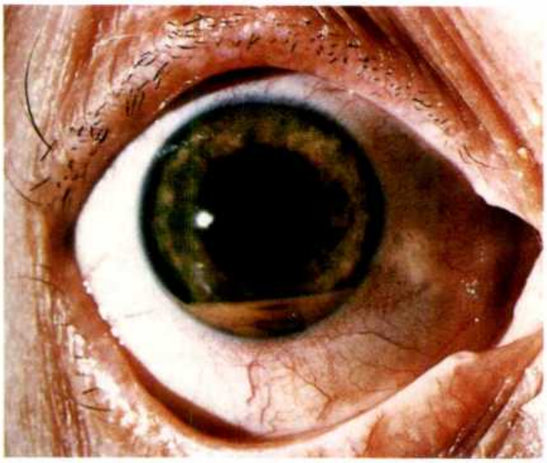

Fig. 1. *'Hyphaema' in case 3 showing the characteristic khaki colour.*

and scanty melanin granules. In addition there are deposits both in the meshwork and on its cameral surface of a light tan-coloured amorphous substance. None of this substance appears to have reached Schlemm's canal.' Sections of the iris showed 'stromal haemorrhages and a minor degree of new vessel formation on the iris surface.' In addition there was 'on the anterior surface of the iris a thin layer composed of red blood cells, leucocytes and some tan-coloured amorphous substance as was present in the meshwork' (C H Greer).

Postoperatively the pressure was controlled, though pilocarpine 2% eyedrops and adrenaline 1% eyedrops were necessary after one week, later being replaced by timolol maleate 0·25% eyedrops.

Over eight years her vision improved to 6/36 with clearing of the vitreous blood, leaving a degenerate liquid vitreous. Her intraocular pressure remained controlled at 20 mmHg with timolol maleate 0·25% eyedrops to the right eye, and the optic disc appears healthy. There is a massive vitreous detachment, with degeneration and syneresis of the vitreous, which superiorly appears shrunken almost to the back of the lens.

Discussion

Of the five phakic patients described prior to the paper of Campbell *et al.*[6] in 1976 four had short intervals of some weeks between the onset of the vitreous haemorrhage and the development of intractable glaucoma, while one case of Phelps and Watzke[4] had a much longer interval of over one year. It remains doubtful whether these earlier cases were due to ghost cells. If they were, the mechanism by which ghost cells migrate from the vitreous cavity to the anterior chamber through an intact vitreous face and lens iris diaphragm is difficult to explain.

In all three of our cases the onset of clinical haemolytic ghost cell glaucoma occurred more than two years after dense vitreous haemorrhage. Clinically the vitreous cavity was loaded with red blood cells and degenerative products, the vitreous itself appearing degenerate. In two cases deepening of the anterior chamber in the affected eye was noted. Campbell and his coworkers[6,9] concluded that ghost cells could not pass through an intact hyaloid face and demonstrated experimentally that such cells layered on the anterior hyaloid face, which appeared to form a barrier to their diffusion from the vitreous into the anterior chamber.

In the patients described here the long-standing vitreous haemorrhage and associated vitreous degeneration may be associated with a functional defect in the anterior hyaloid face and so explain the appearance of ghost cells in the anterior chamber. Cibis[12] considered that degenerate red blood cells might pass into the anterior chamber in patients with ciliary detachment of the vitreous.

These cases are important in their demonstration that haemolytic glaucoma does occur in the presence of an intact lens iris diaphragm, as was confirmed histologically in case 3. Early examination of aqueous aspirates in this condition is valuable. Moreover, the specimens must be filtered with the greatest care to avoid rupturing the cells, as occured in case 1.

The successful treatment of haemolytic glaucoma with anterior chamber washouts has been reported with vitrectomy in recurrent refractory cases.[4,9,13,14] However, treatment by trabeculectomy and anterior chamber washout has not previously been reported; this has the added advantage of long-term control, although some medical therapy was needed for a time postoperatively. In view of the severity of the condition surgery should be used soon after medical treatment has failed, since retention of useful vision is possible.

Haemolytic glaucoma must be differentiated clinically from both haemosiderotic and neovascular (haemorrhagic) glaucoma. Haemosiderotic glaucoma has a more chronic course, with recurrent vitreous bleeding and other signs of haemosiderosis, including retinal degeneration, cataract, iris discolouration, and iron staining of the cornea. However, both conditions may be present in the same eye as in case 3. Neovascular glaucoma is characterised by rubeosis iridis and new vessel formation in the angle.

It may be that a condition of haemolytic glaucoma does occur with an intact lens iris diaphragm and not due to ghost cell obstruction of the drainage angle. However, we believe that true haemolytic ghost cell glaucoma may occur in phakic patients with longstanding massive vitreous haemorrhage and intact lens iris diaphragm as exemplified by these three patients.

We are indebted to the late Dr C H Greer for his kindness in supplying the pathological findings and to the Department of Medical Illustration of the Royal Victorian Eye and Ear Hospital for the clinical photograph. This work was carried out under Research Project 20 of the Royal Victorian Eye and Ear Hospital.

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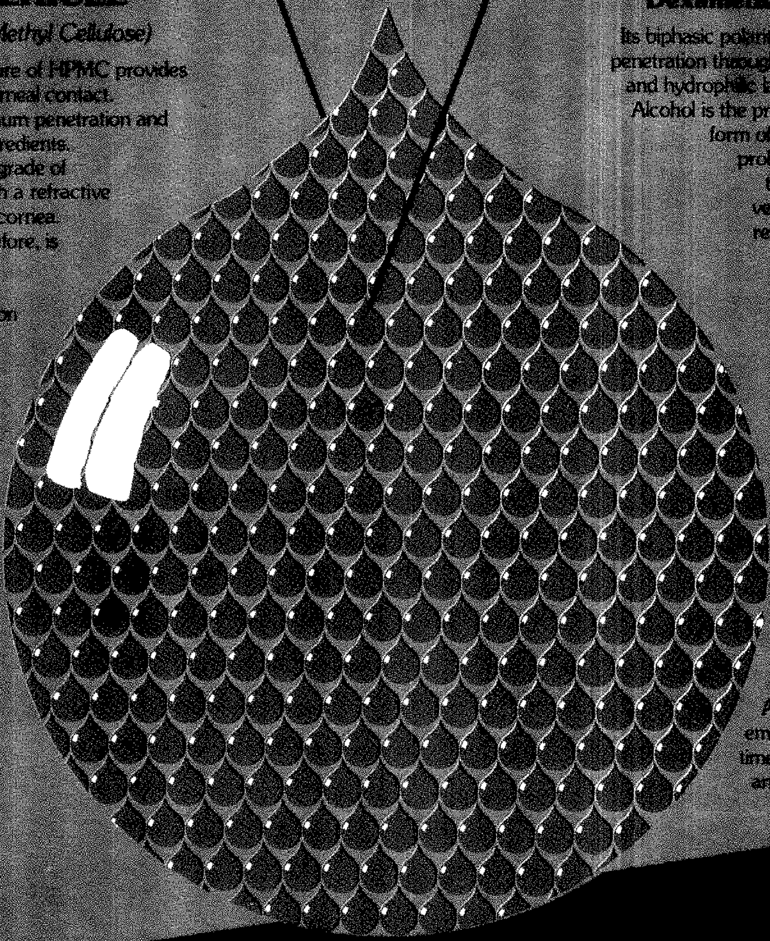

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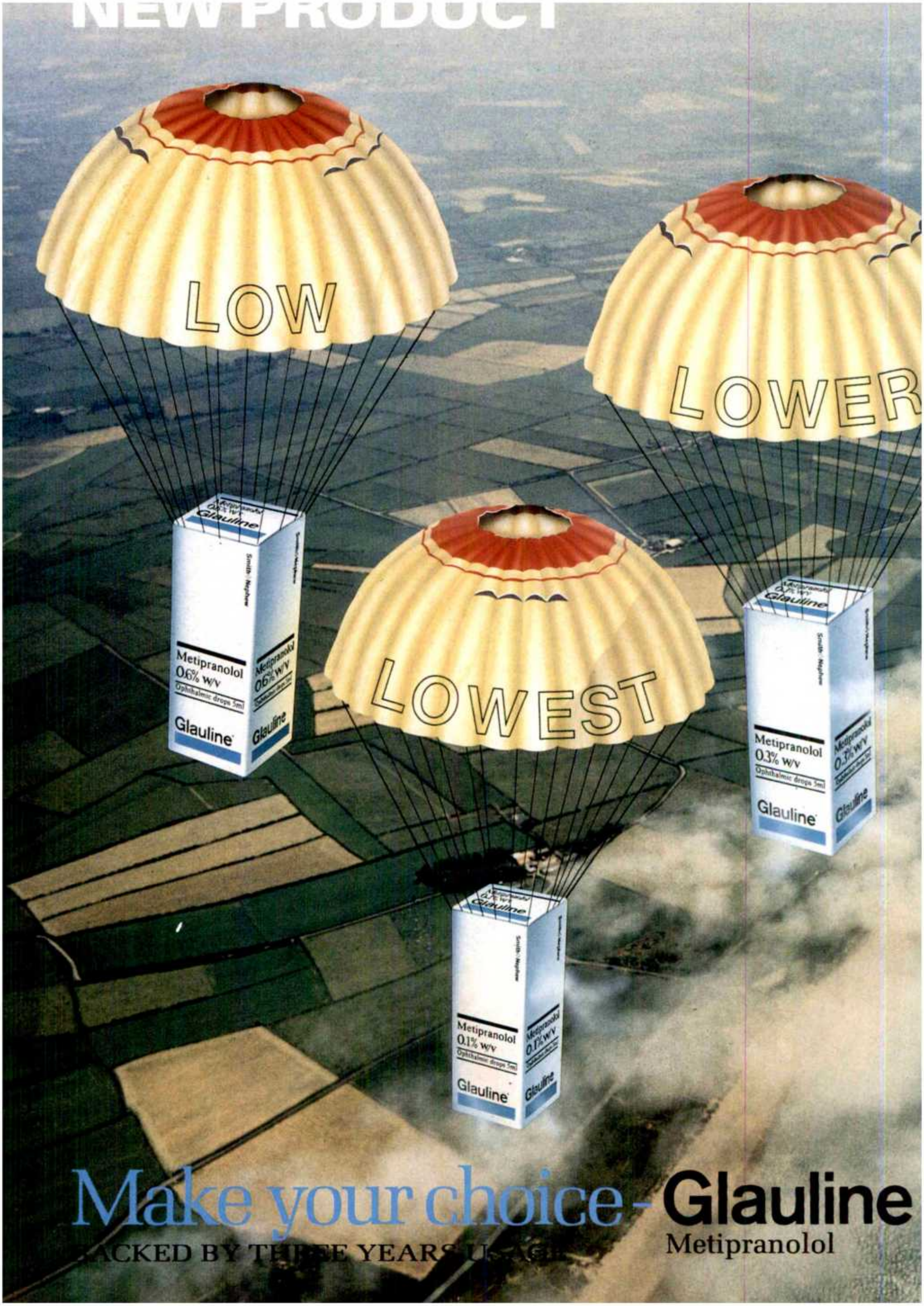
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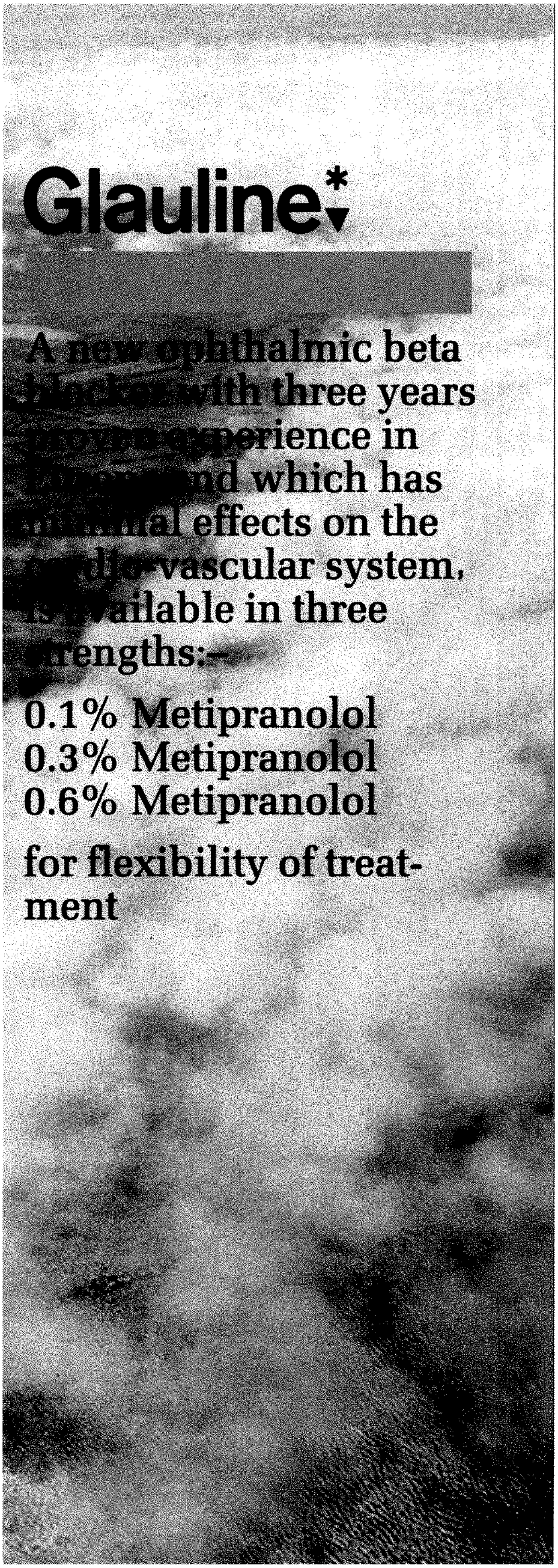

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British Journal of Ophthalmology, 1986, **70**, 607–611

Persistent behavioural blindness after early visual deprivation and active visual rehabilitation: a case report

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SUMMARY Early long lasting binocular deprivation results in behavioural blindness in both man and experimental animals. However, few reported cases show that visual rehabilitation may improve visual behaviour. A 34-year-old man who had experienced 30 years of binocular deprivation due to bilateral cataracts received visual rehabilitation for one year. The rehabilitation included training in eye-hand co-ordination, recognition of objects, evaluation of distance and size, and mobility training. Despite signs of recovery of visual functions the patient never started to use vision in his normal life. The negative outcome of the rehabilitation is partly attributed to the patient's motivational problems and to the relatively short rehabilitation time. Visual rehabilitation may be successful when started immediately after the corrective operation on the eyes when the level of motivation is also high.

Early binocular visual deprivation has a profound effect on the visual behaviour of monkeys and humans after the visual deprivation has ended.[1 2] There are only a few case reports on the recovery from long lasting early blindness.[2-6] The process of potential recovery is always long and difficult.[2 7] Visual rehabilitation was attempted in only two case reports, and it gave encouraging results.[2 7] Electrophysiological studies on visually deprived monkeys have shown that early binocular visual deprivation results in behavioural blindness, though the eyes, the optic nerves, the lateral geniculate nucleus, and the primary visual cortex function well.[8 9] Although there are changes in the function of the primary visual cortex,[8] they do not explain the poor visual behaviour of such animals. It has been shown that early binocular visual deprivation affects the processing of visual signals in the more central parts of the cortex,[1] resulting in difficulty in interpreting visual information.

In our first report of the effects of visual rehabilitation on a patient recovering from long lasting early blindness we described the slow but continuous recovery of the visual functions.[2] Apkarian[6] described the effect of visual training with the aid of the Tactile Vision Substitution system on a girl who had been deprived of form vision from the age of 3 months to 11 years. Despite many difficulties during the training period there was clear evidence of improved visual abilities. These encouraging results induced us to attempt again to enhance the recovery of visual functions of a patient by means of active visual rehabilitation.

Case report

The patient was a 34-year-old man from Zambia. No documents about his early visual status or visual development were available. According to his own report he had become blind at the age of 4 years. The cause of his blindness was unknown, but he had developed bilateral cataracts. He had some visual memories, but it remained uncertain whether his visual status before the blindness had been normal or abnormal. At the age of 16 a bilateral cataract removal was performed and he was given spectacles after the operation. However, they, broke after two months, whereafter he remained without spectacles. He thought that the operation had been a failure and had continued living as a blind person. Despite his handicap he became an educated man in Zambia. He

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learned Braille and studied in a school for the blind. He was found to be a talented student and was given the opportunity to come to Finland to be trained as a teacher for the visually handicapped. We thought that he might have a chance to learn to use his residual vision if he would get proper visual rehabilitation. His motivation to learn to use his sight was diminished because 18 years had elapsed from the time of his cataract operation. Physiologically the time lag meant that the duration of visual deprivation had continued after the corrective operation.

VISUAL STATUS

The patient's visual status before rehabilitation was as follows. The eyes were aphakic. There were no scars from superficial infection and no corneal disease or iritis. Intraocular tensions were normal. The media were clear and the fundi normal except for an inverted disc in the left eye. Refraction in both eyes was +11·0. With aphakic correction vision in the right eye was light perception and some perception of hand movements. In the left eye the vision was perception of the direction of an 8 mm black line at a distance of 3 cm. With respect to colours he could recognise red, blue, yellow, green, and black. As aphakic correction the patient was prescribed spectacles of +13·0.

The visually evoked potential (VEP) was recorded twice during the rehabilitation period. The stimulus was a black-and-white 21·5° × 16·4° square-wave checkerboard pattern. The mean luminance of the checkerboard pattern was 5·5 $cd.m^{-2}$ with a contrast of 95% between the black and white squares. The viewing distance was 100 cm. The checks were reversing at 2 Hz, and analysis was triggered by every second pattern reversal. The electrodes were situated at 01 and 02 and referred to linked ears. In each experimental session we recorded the VEP twice for two different check sizes (7° and 50′). With large checks there was a response through the left eye. There was no response through either eye when small checks were used. The latency for P100 was 148 ms in the first recording session, which took place five months after rehabilitation was initiated. The second VEP was done three months after the first; the latency for P100 had shortened to 120 ms. In the second recording we tested the VEP also to diffuse light flickering once a second. The stimulator was a Grass PS-22 Photostimulator with a mean luminance of 197 $cd.m^{-2}$. The response was normal except for a lengthened latency for P100 (120 ms).

VISUAL BEHAVIOUR BEFORE REHABILITATION

The patient moved about as a blind person using a long cane and tactile exploration. He kept his eyes almost closed and did not pay any visual attention to the surroundings. He read only in Braille. When talking to a person he did not try to look at him. When sitting at a table he made no effort to find things on the table by sight but rather used his hands for exploration. It made no difference to him whether the room was lit or not.

REHABILITATION PROGRAMME

The rehabilitation followed the outlines of the programme described in detail previously.[2] The rehabilitation took place once a week in the Department of Physiology in Helsinki or outdoors in parks and streets. The sessions lasted 1-2 hours. In addition to the authors two other persons contributed to the rehabilitation—Dr Ninel Nezlina (USSR) who was working with SC at the time and Mr Ilkka Linnankoski.

The procedure at the indoor sessions was as follows. The patient was first taught to direct his gaze towards an object and to follow its movement with his eyes. He was taught eye-hand co-ordination using finger paints which enabled him to see the place on paper he had touched with his finger. Later eye-hand co-ordination was sharpened by painting, picking up small things, catching balloons, throwing balls, and by grasping objects near and far. His ability to perceive two and three dimensional forms was developed by showing him pictures of squares, triangles, and circles and by giving him cubes and balls. He was taught to combine visual and tactile information by letting him always touch the objects carefully which he could not initially recognise visually. Later, simple forms were replaced by familiar objects of everyday life (kitchen utensils, pens, books, fruits, etc.). He was taught to evaluate whether an object was near or far, big or small, high or low, thin or thick.

Part of the session was used for mobility training. When indoors he was taught to move about in a room, to recognise open and closed doors, furniture, and windows. When outdoors he was taught to estimate distances, to keep his eyes open continuously, and to pay attention to his feet while walking. During the sessions the patient often told us that he became tired of using his sight and continued to cooperate for two hours at the most. He often wanted to have a short break during which he closed his eyes for a couple of minutes.

The same set of tests which we used to detect possible progress in the first patient's visual abilities[2] were used also with this patient. The tests were: (1) The labyrinth. The patient had to draw a line between two curved lines. (2) A line between two spots. The patient was asked to draw a line from one spot to another. (3) The colouring test. The patient was asked to fill with colour the forms of a triangle, circle, and a square drawn on paper. (4) The picking test. The patient was asked to pick up 20 pellets from a white board as quickly as possible. (5) The post box test. The patient was asked to put eight blocks of four different forms into a box through a cover which had a hole for each form. The tests were performed once a month.

Results

At the beginning the patient was enthusiastic about the rehabilitation, but when he realised that recovery was questionable he became less eager to try to practice. However, he came to the sessions and, despite the difficulties, made some progress.

SIGNS OF PROGRESS

Two weeks after having received the spectacles the patient spontaneously stated that he could no longer stay in a dark room and wanted to turn on the lights to be more aware of the surroundings visually. After 16 weeks from the beginning of the rehabilitation he said that he had for the first time recognised paintings on the walls and had enjoyed looking at them. Later he was given some simple pictures to look at and was able to describe roughly the contents of the pictures. In one picture there was a horse on the lawn. The patient said there was an animal on it. However, he missed all details and had only a faint idea of the contents of the picture. He had learned to recognise kitchen utensils and fruits by sight. For instance, he could distinguish between an orange, a lemon, and a grapefruit and tell by visual inspection whether there was a plum, tomato, or an egg on the table. He learned to recognise practically all the vegetables and fruits available in Finland.

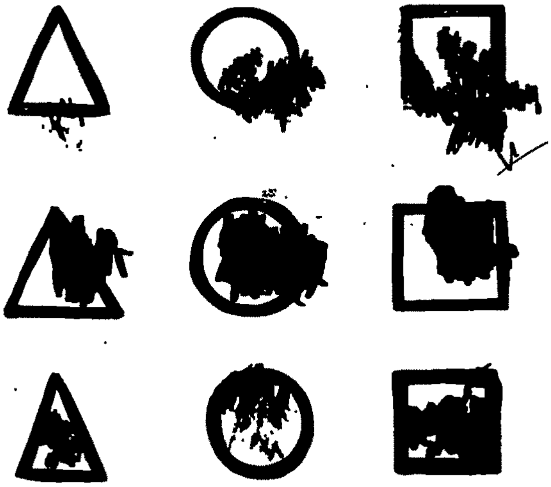

Fig. 1 *The patient's progress in colouring the forms of a triangle, circle and a square is shown. Top forms were coloured after one month, middle forms after four months of rehabilitation, and bottom forms at the end of the rehabilitation.*

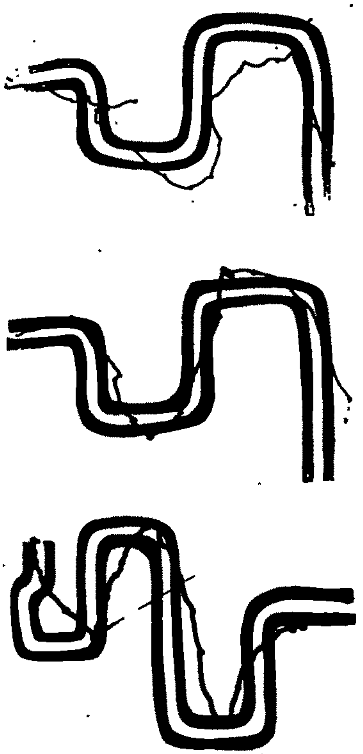

Fig. 2 *The results of the labyrinth test. Top figure shows the performance after one month, middle figure after three months of rehabilitation, and the bottom figure at the end of the rehabilitation.*

RESULTS OF THE TESTS

Colouring test. The patient learned to avoid the contours of the figures but failed to fill the total area of the picture with colour. His progress in colouring the forms can be seen in Fig. 1.

The labyrinth. The patient never learned to master the labyrinth well and was unwilling to perform the task. His progress in this test is shown in Fig. 2.

Post box. The patient gave up trying to perform this test. It was necessary to combine visual and tactile information to master the test. He had to look at the holes on the cover of the box and was allowed to find the right block by exploring the blocks available.

Picking test. The patient's performance in this test is shown graphically in Fig. 3. He was able to grasp

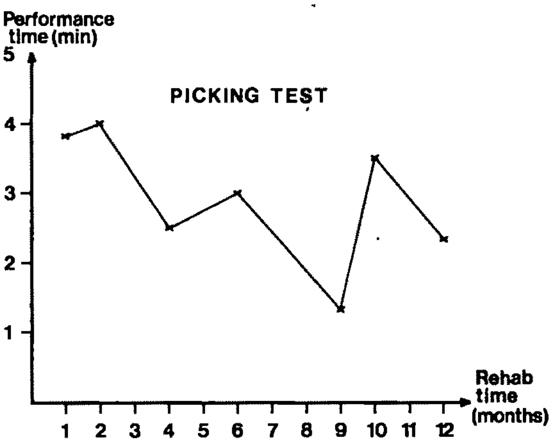

Fig. 3 *The patient's performance in the picking test is shown graphically as a function of the rehabilitation time.*

the pellets with almost complete accuracy and could also see the more distant pellets without great effort. However, his performance varied.

A line between two spots. The patient found it difficult to place his hand accurately on the starting spot. He learned to draw the line fairly well between the two spots, as can be seen in Fig. 4.

When asked to use vision only, the patient was able to avoid bumping into obstacles, and he could find and recognise on the table such objects as books, glasses, and pencils. He could tell how many jars, for instance, there were on the table. But he never used these abilities in his normal life. He could tell just by looking around how many people there were in the room, but he never learned to recognise a person by his looks. When outdoors the patient did not rely on his vision at all and moved about using his cane and preferably the guidance of another person. Sometimes the patient made remarks about the surroundings which indicated that he had visual abilities which were not in active use. Once when we went to the market place he spontaneously asked why there were so many tents there. The tents were the shelters of the salespersons. However, even such incidents did not encourage the patient to continue to use his sight actively; he continued living as a blind person. Thus the final outcome of the rehabilitation, which lasted one year, was negative for the patient.

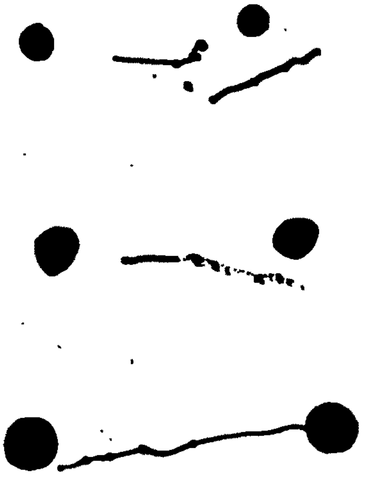

Fig. 4 *Illustration of the patient's ability to draw a line between two spots. Top example was done after two months, middle example after seven months of rehabilitation, and the bottom one at the end of the rehabilitation.*

Discussion

The idea of enhancing the recovery of functions after sensory deprivation by active rehabilitation originated from the results of studies of the effect of visual deprivation on the function of different areas of the central nervous system.

It has been shown that binocular deprivation has a profound effect on the function of the posterior parietal cortex of monkeys[1,10] and on the superior colliculus of cats[11] and rats[12]. The type of functional changes in the cells in these areas is quite similar. The representation of vision decreases and the representation of others modes of perception increases. It seems that during the early sensitive period of life there is competition between the modalities in relation to their influence on the function of the cells in the central nervous system. In the case of binocular visual deprivation, the representation of vision in these areas decreases.

In our first case report of visual rehabilitation[2] the patient showed slow but continuous improvement of her visual functions. The rehabilitation was successful. Contrary to this first experience, the visual behaviour of our second patient did not improve significantly during rehabilitation lasting one year.

The reasons for the negative result are numerous. Our patient came from a culture where emphasis is placed on basic health problems and where it is usually very difficult for a handicapped person to gain a respected position in the society. Since our patient had achieved a fine status as a blind man, he was worried from the beginning about the changes that a partially improved vision might bring about when he returned to his country. This attitude severely affected his motivation to practise and to overcome difficulties during rehabilitation. The long interval between the corrective operation on his eyes and the beginning of the rehabilitation also made him less motivated.

The visual acuity was checked again in the middle of the rehabilitation period and was found to be unchanged. Previously it has been reported that binocular deprivation may arrest the development of visual acuity but does not disrupt the acuity level already established.[13]

On two successive VEP measurements with an interval of three months the latency for P100 shortened from 148 ms. to 120 ms with a patterned stimulus. However, on the basis of this study alone it is not possible to determine the value of VEP as a measure of recovery of visual function. The fact that VEP could be elicited with flash stimuli proves that the primary visual cortex was functioning. It has been suggested that VEP offers a means of testing the residual function of the visual cortex of behaviourally blind patients.[14] Our findings support this idea.

From study of the first patient it was concluded that the improvement in the visual functions was directly related to the amount of practise. It was only after one and a half years that the first patient was able to improve her visual abilities by herself. Accordingly, one year of visual rehabilitation may not have been long enough to encourage the second patient to use his vision continuously to get improved visual functions. During rehabilitation the patient's performance improved in many visual tasks, but his visual functions never developed enough to be useful for him in everyday life.

After early binocular deprivation visual rehabilitation may enhance the recovery of visual functions. However, the longer the deprivation period lasts, the more important it is that the rehabilitation is supportive and continues long enough to assure good results.

We thank Mr Ilkka Linnankoski and Dr Niriel Nezlina for participating in the rehabilitation, and Mrs Katriina Lauren and Mr Raimo Lauren for preparing the pictures. The work was supported by a grant from the Sigrid Juselius Foundation.

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Gyrate atrophy of the choroid and retina: 15 Japanese patients

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SUMMARY We examined 15 Japanese patients who had gyrate atrophy of the choroid and retina with hyperornithinaemia. Their visual acuities fell to 0·2 or worse in the second or third decade of life. Myopia developed late in the first decade, and the refractions decreased to −10 or −15 dioptres at age 20. Tunnel vision developed at approximately age 20. Our results suggested that the visual functions of Japanese patients were worse in the third decade or later than similarly affected Finnish patients.

Simell and Takki[1] first described the association of gyrate atrophy of the choroid and retina with hyperornithinaemia in 1973. Since then much attention has been devoted to this rare inherited disorder. So far about 90 biochemically confirmed cases have been reported in the world literature[2]; about one-third of these are Finnish.[3 4] We present herein the clinical features of 15 Japanese patients with biochemically confirmed gyrate atrophy and hyperornithinaemia and compare them with similarly affected Finnish patients. Some of our cases have been previously reported elsewhere.[5-13]

Patients and methods

Letters inquiring about the existence of patients with gyrate atrophy of the choroid and retina were sent to 80 departments of ophthalmology at universities and medical colleges in Japan in 1984. Replies came from 77 institutions. A total of 15 patients with gyrate atrophy and hyperornithinaemia were identified, and all were re-examined by us. One patient who had been receiving proline for six years (reported as case 1 in an earlier report[6]) and another whose ornithine level in the serum was reduced with vitamin B_6 therapy (case 3 in the same report[6]) were particularly analysed.

The visual acuity for all patients was determined with full correction. Refraction was examined with a streak retinoscope or refractometer. The anterior segment of the eye was observed by slit-lamp examination, and the posterior segment was examined by indirect ophthalmoscopy, biomicroscopic observation with a Goldmann three-mirror lens, and fluorescein angiography. Visual fields were examined by Goldmann perimetry. The serum or plasma ornithine level was determined with a Hitachi amino acid analyser.

Results

Of the 15 patients with gyrate atrophy in Japan 11 were male and four were female. Their ages ranged from 9 to 55 years in 1984. All showed yellowish round patches of atrophy in the peripheral fundus or typical chorioretinal atrophy. Characteristic fundus lesions were confirmed by fluorescein angiography.

Fig. 1 shows the visual acuities of both eyes of each patient according to age. Until age 15 the patients had relatively good central vision, from 0·2 to 1·0, if vitreous haemorrhage had not occurred. The central vision of eyes after vitreous haemorrhage decreased to hand motion or light perception. Visual acuity reduced to 0·2 or worse was found in the second or third decade. Cataract extraction was performed in the third or fourth decade. After cataract extraction the visual acuity increased to various levels (range, 0·03 to 0·6). The subsequent visual impairment was dependent on macular involvement. The patient who received proline for six years[6] had central vision of 1·0 at age 10. The patient who received vitamin B_6

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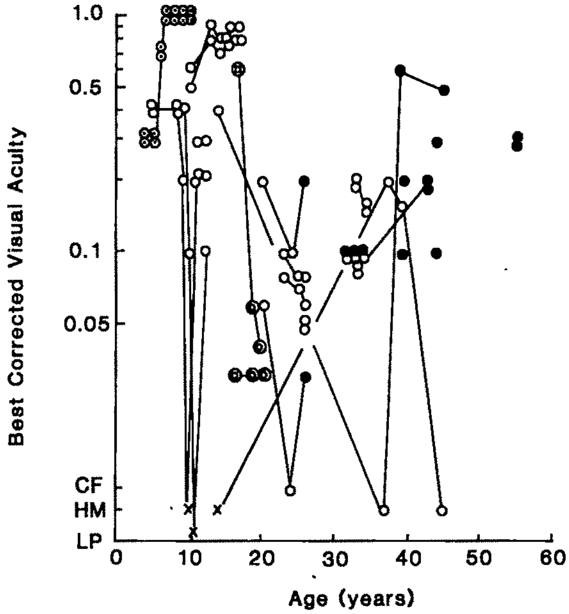

Fig. 1 *Visual acuities of 30 eyes of patients with gyrate atrophy of the choroid and retina. ○ Phakia; ● aphakia; × vitreous haemorrhage; ◉ proline supplemented case; ⊙ vitamin B_6 responsive case.*

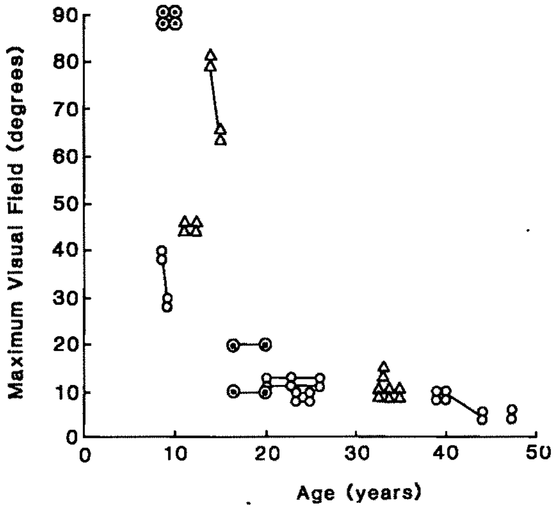

Fig. 3 *Maximum visual fields of 24 eyes of patients with gyrate atrophy of the choroid and retina. ○ male; △ female; ◉ proline supplemented case; ⊙ vitamin B_6 responsive case.*

showed reduced central vision in spite of the therapy.

Fig. 2 shows the refractions of 21 phakic eyes by age. Myopia developed late in the first decade, and refractions declined to −10 or −15 dioptres by age 20. The patient who received proline had the smallest refractive error. The vitamin B_6 responsive patient experienced no change in refraction due to the vitamin therapy.

Fig. 3 demonstrates the decreasing of visual fields with age in 24 eyes. Tunnel vision developed at approximately age 20. No difference in visual field was noted between males and females. The visual

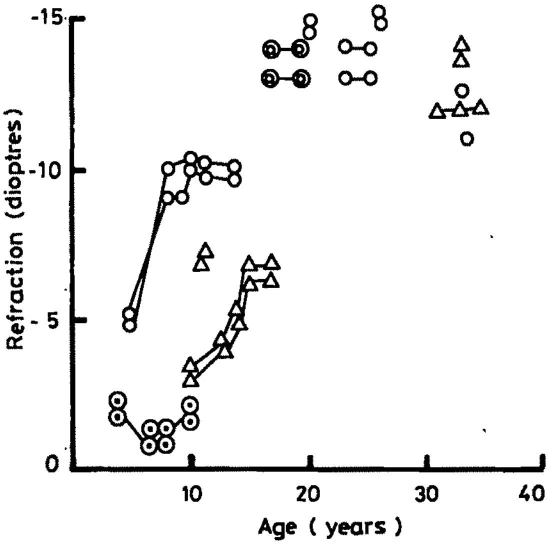

Fig. 2 *Refractions of 21 phakic eyes of patients with gyrate atrophy of the choroid and retina. ○ male; △ female; ◉ proline supplemented case; ⊙ vitamin B_6 responsive case.*

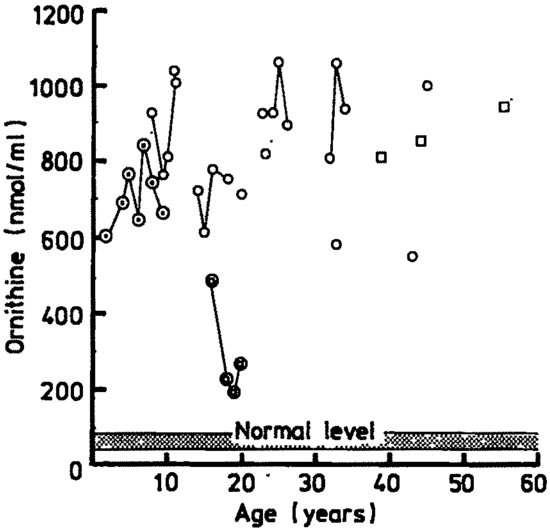

Fig. 4 *Serum or plasma ornithine levels in 15 patients with gyrate atrophy of the choroid and retina. ○ serum; □ plasma; ◉ proline supplemented case; ⊙ vitamin B_6 responsive case. (nmol/ml=mmol/l.)*

fields of the patient who received proline were full. The vitamin B_6 responsive patient showed no change in visual field from the therapy.

Fig. 4 shows the serum or plasma ornithine levels in 15 cases. The ornithine levels, which ranged from 500 to 1100 mmol/l in patient on a regular diet, did not change with age. The serum ornithine levels in the patient receiving proline were unchanged. In the vitamin B_6 responsive patient the serum ornithine level decreased with oral administration of the vitamin, as shown previously.[5]

Of the 15 cases, parental consanguinity was present in eight, absent in four, and unconfirmed in three.

Discussion

Patients were identified from the replies received from our letters of inquiry. Although all Japanese patients were not included in this present study, it is possible that nearly all cases of gyrate atrophy might have been represented.

Takki and Milton reported on the natural history of 27 Finnish patients with gyrate atrophy.[4] Differences in central and peripheral vision were noted between their Finnish and our Japanese patients. The central vision in phakic Japanese patients at age 20 or later was below 0·2, or worse than that in the Finnish patients. François observed that 'visual acuity may remain rather good for a long time' in his review of gyrate atrophy.[14] It is likely that his data were based on reports excluding Japanese cases. Severe constriction of visual fields developed in the Japanese patients at about age 20, while tunnel vision proceeded in the Finnish patients to the fourth or fifth decade.[4] Takki and Milton[4] showed that some women retained larger visual fields. The Japanese patients showed no difference in the deterioration of peripheral vision between males and females. Possibly the visual functions of Japanese patients with gyrate atrophy in the third decade or later were more deteriorated than those of Finnish patients. However, why deficient activity of ornithine-ketoacid-transaminase has the different visual effects remains obscure.

The patient who received proline for six years showed good central and peripheral vision and mild myopia. The vitamin B_6 responsive patient, however, had no improvement in vision, though the therapy reduced the patient's serum ornithine level.

The reason for a predominance of male patients (11 to 4) in our series was unknown. Consanguinity of the patients' parents was found in half the cases, suggesting a recessive trait.

The authors would like to thank the 77 departments of ophthalmology at universities and medical colleges in Japan for replying to our inquiry. We also thank Ms M Gere for editing the manuscript. This study was supported in part by grants from the Ministry of Education and the Ministry of Health and Welfare, Japan.

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Serology in ocular toxoplasmosis

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SUMMARY The diagnostic value of toxoplasma serology in ocular disease was evaluated in the following groups of patients: (I) uveitis cases of various causes (n=291); (II) consecutive posterior and panuveitis patients (n=60); (III) patients with definite congenital and ocular toxoplasmosis (n=8); (IV) cases of clinical ocular toxoplasmosis (n=25); and control patients with uveitis of non-toxoplasma origin (n=12). No relation was observed between the level of the dye test titres and the diagnosis of ocular toxoplasmosis (groups I and II). During the active stages of the disease no typical change of the titres occurred in several longitudinally studied patients with toxoplasmosis. In group III one case was discovered to be negative by the dye test despite active ocular disease; however, IgG antibodies against toxoplasma were detected by the ELISA technique. In group IV, which was investigated by the ELISA technique, 100% of the toxoplasmosis patients were positive for IgG versus 58% of the control patients. Circulating immune complexes containing IgG and toxoplasma antigen were detected in seven of 25 toxoplasmosis patients (28%) and in two of 12 control patients (16%). Our study shows that the definite diagnosis of ocular toxoplasmosis or its exclusion by serological means only is not yet feasible. The possible superiority of the ELISA test to the dye test warrants further investigation.

Toxoplasma retinochoroiditis has been reported as a leading cause of posterior uveitis.[1] Two clinical forms of toxoplasma infection are recognised, namely, a congenital and a postnatally acquired disease. In the case of acquired toxoplasmosis, which rarely causes ocular disease,[2] the antibody titres are usually very high, and therefore serology for this diagnosis is indispensable.

The diagnosis of ocular toxoplasmosis, which is generally accepted to be a congenital disease,[3] may be very difficult. The conclusive diagnosis of active toxoplasmosis depends on the isolation of toxoplasma organisms from the fluid or tissue of the patient suffering from an active form of the disease, but this is rarely possible in ocular disease. The high incidence of IgG antibodies against toxoplasma in the population is mostly due to a past acquired infection; therefore a positive IgG test is not discriminatory for the ocular disease and may not be related to the eye lesion. Most authors agree that a positive test by any of the accepted serological methods is compatible with the diagnosis of ocular toxoplasmosis.[2,4,5] A negative test is thought to rule out the diagnosis of ocular toxoplasmosis,[6] and therefore ophthalmologists have often urged tests to be performed even on undiluted serum. On the other hand cases of histologically proved toxoplasma retinitis have been described with negative serum titres against toxoplasma.[7]

Several authors have suggested that demonstrating the local synthesis of toxoplasma antibodies in the eye is proof of the diagnosis of ocular toxoplasmosis.[8-10] But this procedure is not yet routinely performed, and the diagnosis of ocular toxoplasmosis is often based on the typical clinical picture in combination with various serological findings.

Since no well documented evidence is available on the value of toxoplasma serology in ocular disease, we have evaluated the serological findings in a large number of patients attending uveitis clinics, as well as in a longitudinal study of children with a definite congenital toxoplasmosis. Special attention was paid to the following points: the diagnostic value of a positive test in case of ocular toxoplasmosis; the

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possible exclusion of this diagnosis by a negative test result; and possible distinctions among several tests in current use, namely, the dye test, complement fixation reaction (CRF), and enzyme linked immunosorbent assays (ELISA) for toxoplasma antibodies, free toxoplasma antigen, and toxoplasma-containing immune complexes.

Patients and methods

Four patient groups with partial overlap were studied for toxoplasma serology.

Group I consisted of 291 uveitis patients attending uveitis clinics of the university eye hospitals in Amsterdam and Rotterdam during 1981 and 1982. These patients suffered from uveitis of various causes. For a more detailed evaluation we selected from group I a subgroup of 60 consecutive patients suffering from posterior uveitis or panuveitis in Amsterdam during 1982 (group II). The third group (III) of patients consisted of eight young adults known to have definite congenital and ocular toxoplasmosis. These eight patients are part of a prospective study based on 1821 pregnant women[11] and include all cases of definite congenital and ocular toxoplasmosis, in whom a longitudinal serological follow-up was available. The fourth group (IV) consisted of 25 patients with a clinical diagnosis of ocular toxoplasmosis and 12 control patients with uveitis of non-toxoplasma origin.

The serological tests employed in all four groups included the Sabin-Feldman dye test and complement fixation reaction (CRF). These tests were performed according to standard techniques in the Royal Tropical Institute in Amsterdam.[12] Unfortunately not all our samples were determined by the dye test in very low dilutions or even in undiluted serum. This procedure is not a laboratory routine and is performed only when specially requested. In groups III and IV the enzyme linked immunosorbent assay for IgG and IgM toxoplasma antibodies and tests for detecting free toxoplasma antigen and circulating immune complexes containing toxoplasma antigen were performed as described elsewhere.[13-15]

The serology in all patients of groups I, II, and IV was done during an active stage of their ocular disease, whereas the blood samples in group III were obtained independently of ocular disease.

The clinical diagnosis of ocular toxoplasmosis was based on ophthalmological examination, showing active unilateral focal necrotising retinochoroiditis, often in satellite formation, with associated vitreous inflammation, and also the appearance of pigmented scars after clearing of the vitreous.[4]

The diagnosis of definite congenital toxoplasmosis in children was based on the following criteria: seroconversion of the mother during pregnancy, and persistence of positive dye test titres beyond the age of 30 months as defined in an earlier study.[11]

Statistical analysis was performed by the χ^2 test and Kolmogorov-Smirnov test for consistency of frequency distributions.[16]

Results

Group I: 291 uveitis patients

To determine whether it is worthwhile to use toxoplasma serology as a screening tool in diagnosing uveitis patients we reviewed the medical records of 291 uveitis patients (group I). The mean age of these patients was 42·4 years (range 9 and 92 years) and the male to female ratio was 1:0·88. The patients were subdivided into three categories according to the localisation of their uveitis: anterior uveitis (n=144), panuveitis (n=71), and posterior uveitis (n=76). The distribution of the dye test titres in all these forms of uveitis was identical (Kolmogorov-Smirnov test) (Fig. 1). Nearly all the patients with clinical ocular toxoplasmosis (n=32) suffered from posterior uveitis.

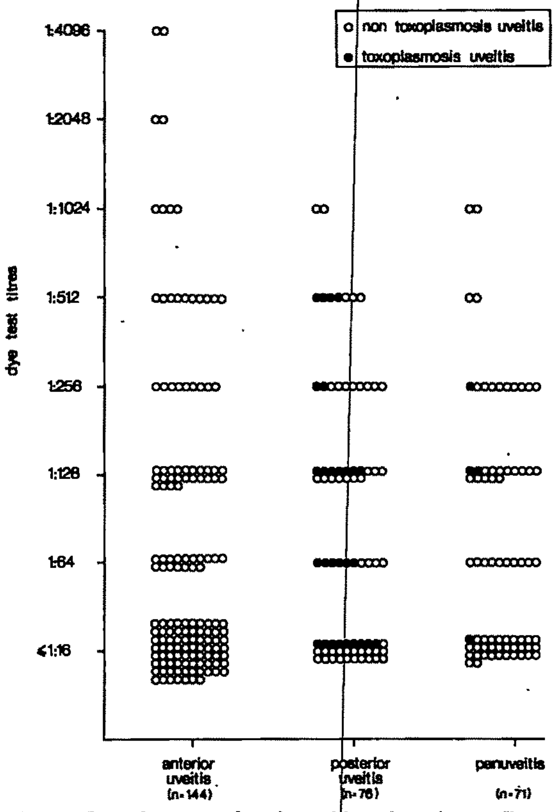

Fig. 1 *Toxoplasma serology in uveitis patients (group I).*

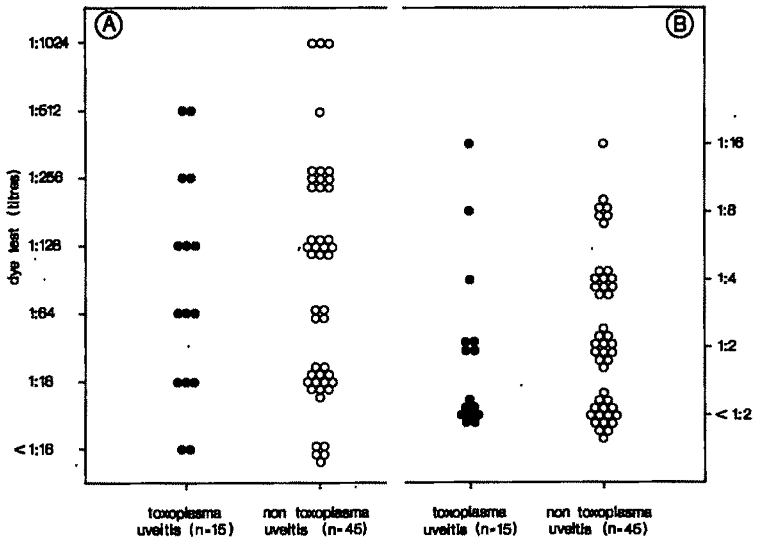

Fig. 2 *Toxoplasma serology in posterior uveitis and panuveitis patients (group II).* A: *dye test;* B: *complement fixation test.*

In the posterior uveitis group a similar distribution of the dye test titres was found in the toxoplasmosis and the non-toxoplasmosis patients. No correlation was found between the level of the titre and the clinical diagnosis.

Group II: 60 consecutive posterior uveitis and panuveitis patients

To discover whether toxoplasma serology correlates with the clinical diagnosis and therefore could be of diagnostic value in a more restricted group of patients we analysed 60 consecutive patients with posterior uveitis and panuveitis in more detail (group II). This group included 15 clinical cases of ocular toxoplasmosis. The titre distribution of the dye test and complement fixation reaction in the toxoplasmosis and the non-toxoplasmosis groups showed a similar pattern (no significant difference found by Kolmogorov-Smirnov test) (Fig. 2). The toxoplasmosis patients were aged 10 to 40 years. We therefore studied the relationship between the dye test, complement fixation reaction titres, and the age of the patient (Fig. 3) to determine whether serology could be more valuable in a certain age group. Even in the young patients no correlation was found between the level of the titre and the clinical diagnosis of toxoplasmosis. Out of the six patients with a raised dye test titre ($\geq$1:512) two had ocular toxoplasmosis, while two more out of nine patients with a raised complement fixation reaction ($\geq$1:8) suffered from this disease.

In several patients of group II the dye test titres were monitored with an interval of three weeks to see whether a change of titre could be found, and, if it was, to see whether a rise of the titre could be found only in the toxoplasmosis patients. The longitudinal follow-up during the course of the uveitis, however,

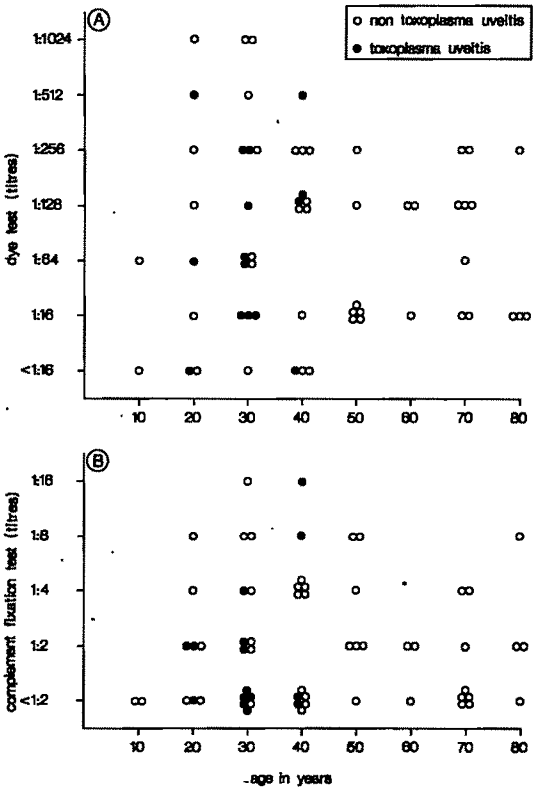

Fig. 3 *Relation between toxoplasma serology and age in posterior uveitis and panuveitis patients (group II).* A: *dye test;* B: *complement fixation test.*

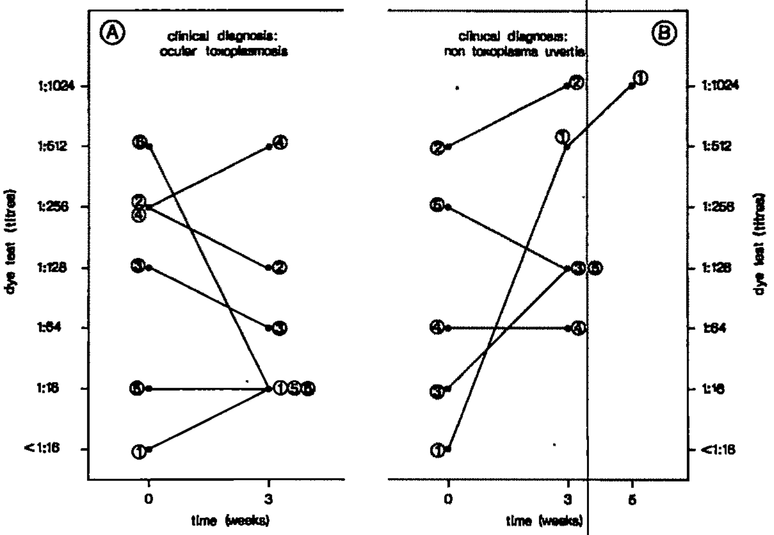

Fig. 4 *Longitudinal follow-up of toxoplasma antibodies in uveitis patients (group II). The numbers indicate individual patients.*

showed an extremely variable course of the dye test titre in both the toxoplasmosis and the non-toxoplasmosis groups (Fig. 4). Patient no. 1 of the non-toxoplasmosis group was the only patient who showed an evident rise in titre. He had probably been infected or reinfected owing to his poor general condition. Ophthalmologically he presented with bilateral retinitis during subacute sclerosing panencephalitis; there was no clinical resemblance to ocular toxoplasmosis. Patient no. 6 of the toxoplasmosis group showed a sharp decline of his dye test titre.

Group III: eight cases of definite ocular toxoplasmosis (longitudinal study)

To ascertain whether the absence of toxoplasma antibodies indicates that an ocular toxoplasma infection is highly improbable, we reviewed the dye test titres in eight young adult patients with known congenital and ocular toxoplasmosis. These patients are a part of a big prospective study of children born from mothers with a seroconversion during pregnancy.[11] Most children were followed up annually until the age of 20 years by an ophthalmological as well as a laboratory investigation. The fluctuation of their titres is shown in Fig. 5. There was one boy (case no. 7) with ocular toxoplasmosis and a negative dye test titre. A more detailed laboratory investigation was performed when the children were 18 years old (Table 1). At that age all the patients had positive IgG antibodies against toxoplasma as measured by an ELISA technique, though in one case no antibodies were detectable by the Sabin-Feldman dye test.

Group IV: 25 cases of clinical ocular toxoplasmosis and 12 control patients with non-toxoplasma uveitis

To investigate whether the newer, currently applied serological methods have the same limitations as the

Table 1 *Toxoplasma serology in eight cases of congenital and ocular toxoplasmosis at the age of 18 years (group III)*

Pat. no.	*Dye test*	*CFR*	*ELISA*				
			IgG	*IgM*	*Circ.Ag*	*CIC cont.IgG*	*CIC cont.IgM*
1	1:4096	1:32	+	–	–	–	–
2	1:4	negative	+	–	–	–	–
3	1:64	negative	+	–	–	–	–
4	1:128	1:2	+	–	–	–	–
5	1:64	1:2	+	–	–	–	–
6	1:16	negative	+	–	–	–	–
7	negative	negative	+	–	–	–	–
8	1:64	negative	+	–	–	–	–

CFR=complement fixation reaction; circ.Ag=circulating antigen; CIC cont.IgG=circulating immune complexes containing toxoplasma antigen and IgG; CIC cont.IgM=circulating immune complexes containing toxoplasma antigen and IgM.

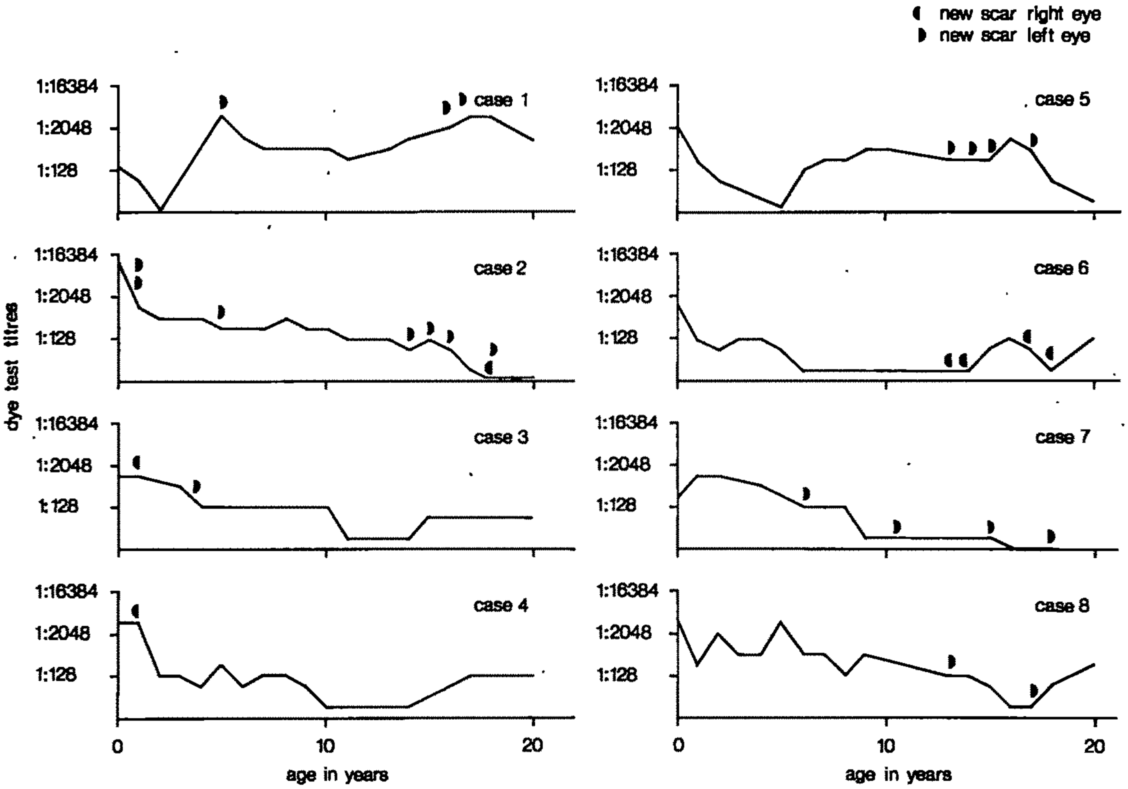

Fig. 5 *The course of the dye test titre in eight patients with definite congenital and ocular toxoplasmosis (group III).*

dye test we compared serological data obtained by the ELISA technique from 25 patients with ocular toxoplasmosis and 12 controls with non-toxoplasma uveitis. The mean age in the toxoplasmosis group was 29·2 years (range 16 and 47 years) and the male to female ratio was 1:1·18. In the control group the mean age was 31·9 years (range 16 to 47 years) and the male to female ratio was 1:0·7.

All patients in the toxoplasmosis group were positive for IgG antibodies by the ELISA technique, which was in accordance with their dye test titres (Table 2). There were four cases, however, in which a comparison was impossible because the dye test titres were not determined in undiluted serum.

In the non-toxoplasmosis group only seven patients (58%) were positive for IgG antibodies by ELISA. Of these seven patients six had positive dye test titres; the remaining patient was not examined by this technique. None of the patients in either group had detectable IgM antibodies or free toxoplasma antigen in the circulation. Circulating immune complexes containing IgG antibodies were found in seven toxoplasmosis patients (28%) and in two control cases (16%). These two patients were diagnosed as having heterochromic cyclitis of Fuchs and bilateral retinal vasculitis of unknown origin respectively. Circulating immune complexes containing IgM antibodies were found in the patient with heterochromic cyclitis.

Discussion

From the data presented in this study it can be concluded that classical serology (dye test) is of little value when screening uveitis patients. A positive test (independent of the titre) does not prove the diagnosis and a negative result may not exclude it.

The clinical value of a positive test result is dependent on the prevalence of positive tests in the population, the age of the patient, and the specificity and sensitivity of the test employed.[2] In the Netherlands more than 60% of the population in the third and fourth decades have been shown to be positive for antitoxoplasma antibodies.[17] It is not possible to determine whether the antibodies found are related to the eye lesion or whether they are a coincidental finding.[9] In the clinical situation the presence of antibodies indicates only that the patient has been infected by toxoplasma organisms. Nearly all toxoplasmosis patients in our study had low positive dye test titres, and no correlation was found between the

Table 2 *Toxoplasma serology by ELISA in 25 cases of clinical ocular toxoplasmosis and 12 control cases (group IV)*

Case no.	*Sex, age*	*Dye test*	*ELISA*				
			IgG	*IgM*	*circ.Ag*	*CIC cont.IgG*	*CIC cont.IgM*
Toxoplasmosis patients							
1	F39	1:512	+	–	–	–	–
2	M19	1:512	+	–	–	+	–
3	F19	1:256	+	–	–	+	–
4	F24	1:256	+	–	–	–	–
5	F40	1:256	+	–	–	–	–
6	M28	1:256	+	–	–	+	–
7	F25	1:128	+	–	–	–	–
8	F37	1:128	+	–	–	–	–
9	F38	1:128	+	–	–	–	–
10	M25	1:128	+	–	–	–	–
11	M32	1:128	+	–	–	+	–
12	M38	1:128	+	–	–	–	–
13	F18	1:64	+	–	–	–	–
14	F30	1:64	+	–	–	–	–
15	F32	1:64	+	–	–	–	–
16	M19	1:64	+	–	–	–	–
17	F29	1:16	+	–	–	+	–
18	F30	1:16	+	–	–	–	–
19	F37	1:16	+	–	–	+	–
20	M16	1:16	+	–	–	+	–
21	M47	1:16	+	–	–	–	–
22	F23	<1:128	+	–	–	–	–
23	F29	<1:16	+	–	–	–	–
24	F34	<1:16	+	–	–	–	–
25	M23	<1:16	+	–	–	–	–
Control patients							
1	M29	1:512	+	–	–	+	–
2	M31	1:256	+	–	–	–	–
3	F41	1:128	+	–	–	–	–
4	M38	1:64	+	–	–	–	–
5	M47	1:64	+	–	–	–	–
6	F28	1:16	+	–	–	–	–
7	M16	<1:16	–	–	–	–	–
8	M31	not done	–	–	–	–	–
9	F31	not done	–	–	–	–	–
10	F32	not done	–	–	–	–	–
11	F35	not done	+	–	–	+	+
12	M24	not done	–	–	–	–	–

circ.Ag=circulating antigen; CIC cont.IgG=circulating immune complexes containing toxoplasma antigen and IgG; CIC cont.IgM=circulating immune complexes containing toxoplasma antigen and IgM.

level of the titre and the clinical diagnosis. These findings are in agreement with those of other authors.[2,6]

In the adults with clinical ocular toxoplasmosis (group II), who were followed up longitudinally, as well as in the congenitally infected children with ocular toxoplasmosis (group III) no correlation was found between the toxoplasma antibody titre and the activity of the ocular disease, which confirms previous observations.[4,5] A decline in the dye test titre during acute ocular disease was observed in one patient (case no. 6, toxoplasmosis patients, group II). This change could be explained by the formation of immune complexes containing toxoplasma antibodies. It is not possible to determine whether the changes in the titre are due to ocular disease or to the basic fluctuations of the titre, or whether they are related to the activity of the disease elsewhere in the body.[18] The antibody titre in serum is dependent on antigenic stimulation in the body as a whole, and this can be very low or even absent in cases of ocular inflammation.[6,8,11] It is evident that in the case of ocular toxoplasmosis the level of the titre has no diagnostic value. On the other hand Vadot[19] has recently reported that the presence of low dye test titres in patients with toxoplasma retinochoroiditis was associated with a higher recurrence rate when compared with cases of high dye test titres. The clinical relevance of these findings deserves further study.

Our data on positive dye test titres show that the only important result of a test in cases of ocular toxoplasmosis in adults should be the negative one. The clinical relevance of the negative antibody test is related to the sensitivity of the test used. Several cases of histologically proved ocular toxoplasmosis with a negative dye test have been reported. The two classical examples of a negative dye test despite proved ocular toxoplasmosis[20,21] were in reality cases with unknown but certainly low dye test titres. In a case described by Zscheille[20] the patient's dye test was negative at a dilution of 1:16 and Franceschetti and Englebrecht's[21] patient had a negative dye test at a dilution of 1:25. Blood samples from neither of these patients were tested in lower dilutions. Ikuy *et al.*[7] isolated toxoplasma organisms from the cerebrospinal fluid of a patient with clinical ocular toxoplasmosis and found his dye test negative with undiluted serum. Our own case of a negative dye test with undiluted serum was observed in a boy with definite congenital and ocular toxoplasmosis at the age of 16 years (case no. 7, group III). The dye test of this patient remained negative despite the reactivation of his ocular disease. However, he was found to be positive for IgG antitoxoplasma antibodies when tested by ELISA.

The Sabin-Feldman dye test was the first reliable test developed and was a standard by which other tests were judged. However, live toxoplasma organisms are employed, and special laboratory precautions must be taken to perform this test. For this reason the dye test became unpopular[5,6] and other tests were developed.

Our finding shows that the dye test may be negative in ocular toxoplasmosis. This limitation does not seem to apply to the ELISA technique. With ELISA all our clinical toxoplasmosis cases (group III and IV) were positive for IgG antitoxoplasma antibodies, whereas the control patients (group IV) were found to be positive in 58%, which difference is highly significant ($p<0\cdot01$). Our findings suggest that the ELISA is more sensitive than the dye test, which is in agreement with several other studies, where the sensitivity of the ELISA is higher, especially when dealing with low positive titres.[22,23] Since our patients were more extensively studied by means of the dye test, this observation needs further investigation.

The detection of circulating antigen or circulating immune complexes containing toxoplasma antigens which can be found for a short time during a fresh infection or reinfection is promising.[13,15] However, in our study of 25 patients with ocular toxoplasmosis we could not find any free circulating antigen. Circulating immune complexes containing IgG antibodies were found in 28% of ocular toxoplasmosis patients and in 16% of controls. This difference is not statistically significant, though it should be remembered that the number of patients was very small and that active toxoplasma infection in immune complex positive control patients cannot be excluded.

Such a serological diagnosis of active toxoplasma infection was made in one patient with heterochromic cyclitis of Fuchs. This patient also had an old retinal toxoplasmosis scar, which was certainly not active. The association between toxoplasmosis and heterochromic cyclitis has already been noted.[24,25] Whether the serological findings in the patient presented here are coincidental or are evidence of a relationship between active toxoplasmosis and heterochromic cyclitis deserves further investigation.

We conclude that a definite diagnosis of ocular toxoplasmosis by serological means only is not yet feasible. The possible superiority of the ELISA test to the dye test warrants further investigation. In cases of doubt other diagnostic tests, such as detection of local antibody production, should be used. The final conclusion of this study is that a negative test result with undiluted serum indicates that ocular toxoplasmosis is highly improbable

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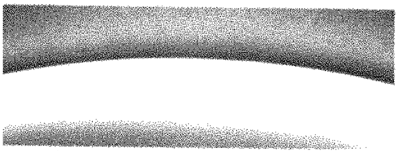

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A study to assess the value of Dacron slings in the management of squints which are not amenable to conventional surgery

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SUMMARY Loops of non-absorbable sutures were used to extend the recession of the horizontal recti in 27 patients. All patients had horizontal squints and were considered unsuitable for conventional recession/resection procedures. The technique is described and the results are evaluated.

Certain patients present difficulties in the surgical management of their squint. These patients may be divided into four main categories. (1) Patients who have an unsatisfactory residual deviation, where both medial recti have been maximally recessed (5–6 mm) in convergent squint, or both lateral recti maximally recessed in divergent squint. (2) Patients with an unacceptable residual deviation, where the squinting eye has already had maximal conventional muscle surgery and it is considered unwise to operate on the fellow eye when this eye is the only eye with good vision. (3) Patients who have not had previous surgery but whose angle of squint is so large that it cannot be corrected by a conventional recession/resection procedure on the squinting eye and the fellow eye is the only eye with good vision. (4) Certain cases of paralytic squint where a very large angle of correction is required.

These were the criteria for the type of surgery performed on the 27 patients included in this series.

There is a limit to the position the horizontal recti can be recessed beyond which the action of the muscle is jeopardised, resulting in unwanted significant restriction of ocular movement. Marginal myotomy, though rarely used as a primary procedure, is often the operation chosen to weaken the appropriate muscle. Marginal myotomy has, however, been described by Von Noorden as a crippling procedure, reducing the number of contractile fibres, and, should overcorrection occur, he states that it is a 'nearly insurmountable surgical complication'.[1] Furthermore the operation is difficult to quantify.[2]

A number of alternative approaches have been described. Nolan[3] has suggested a muscle lengthening operation, a modification of that described by Gonin in 1911.[4] Mittleman and Folk[5] suggested recessing the muscle beyond the conventional 5–6 mm to a point 13·5 mm from the limbus. Chavasse[6] used electrocoagulation across the muscle width to render the anterior portion non-contractile and so weaken its action, and Morales *et al.*[7] lengthened muscles with a silicone implant. In the event of a persistent convergence excess esotropia Von Noorden performed a Faden operation (posterior fixation suture) with good results.[2]

Gobin[8] described the use of Dacron slings to obtain large recessions. We have adopted this technique and found it to be safe and effective; it has many advantages over the aforementioned procedures.

Patients and methods

Twenty-seven patients who had undergone a recession of one or more of their horizontal recti with 3–4 mm loops of non-absorbable suture were assessed. There were 17 males and 10 females. Their age at the time of surgery ranged from 2 to 60 years, mean 19 years. Seventeen patients had surgery for concomitant esotropia, seven for concomitant exotropia, and three for paralytic squint. Twelve of the 24 patients with non-paralytic squint had already had maximal surgery (rectus recessions of more than 5 mm) on both eyes; nine of the 24 had already had maximal surgery on their squinting eye and the fellow eye was their only good seeing eye; three had not had previous surgery but had large deviations and only

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one eye with good vision (the deviation was so great that it could not be corrected by conventional recession/resection surgery to the one eye). The majority of the cases (67%) each having had previous squint surgery with poor cosmetic results, were referred from other units to one of the surgeons (RT).

All patients had orthoptic assessments before and after surgery. Table 1 summarises the findings and surgical procedures. Patients who had previously been discharged were recalled for up-to-date assessment, and where possible the degree of limitation of movement was assessed by the maximal excursion of the eye as measured on the synoptophore, as in the method described by Urist[9] except quantified more accurately.

The operation was performed by a standard limbal approach and the muscle identified. 5/0 Dacron sutures were used to secure the muscle and it was then divided from its insertion. The suture needle was passed through the sclera the requisite number of millimetres from the previous insertion, and from this point the muscle was allowed to slip backwards 3 mm and the suture tied. Thus the muscle could retract backwards from the new insertion on a 'Dacron sling' (Fig. 1) in a manner similar to that described by Gobin.[10]

In 23 of the cases the recession was combined with a resection of the ipsilateral antagonist (except case 21, where a bilateral lateral rectus recession was employed with a Dacron sling to recess the right lateral rectus). In the remaining four cases (1, 4, 15, and 23) only a recession with a Dacron sling was performed.

Results

Most of the patients achieved an excellent cosmetic result. The mean change in angle was 38 prism dioptres (PD) for near and 33 PD for distance, ranging from 4 PD to 105 PD. Three cases (25, 26, 27) had paralytic squints, but the Dacron sling procedure was only part of the surgical management planned. If these three cases are excluded, the mean change in angle was 37 PD for near and 33 PD for distance. Case 19 was initially improved, but at the last assessment the angle of squint had returned to around the preoperative value. Further surgery was offered but declined. Case 6 had an original sling procedure that corrected 35 PD for near and 53 PD for distance, but the results of the secondary sling were much less, correcting 10 PD and 4 PD for near and distance respectively.

Follow-up ranged from 1 month to 7 years, with a mean of 1 year 10 months.

Muscle function tests showed some weakness of action in most of the cases, though this did not affect the cosmetic appearance. Medial rectus action in esotropias had a postoperative range of 25° to 40° with a mean of 33° and lateral rectus function in exotropias a range of 30° to 40° with a mean of 36° (Table 2).

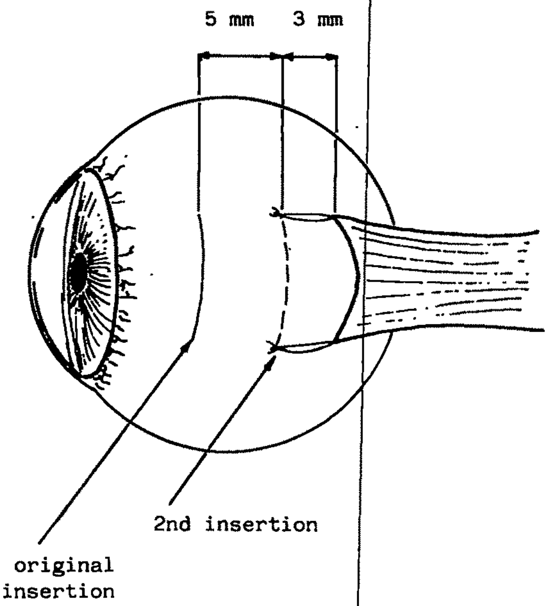

Fig. 1 *Recession with Dacron slings on which the muscle retracts backwards 3 mm.*

Discussion

The definition of a good cosmetic result is somewhat arbitrary. Marshall Parks[11] aims for a postoperative angle of 15 PD of esotropia or less in cosmetic convergent squint surgery. All but one of the esotropias in this study were less than 15 PD postoperatively and would thus qualify as a success. Exotropias are often more noticeable, and a smaller residual angle should be sought. It is obvious from Fig. 2 that the majority of divergent squints had a less than favourable result, though most were cosmetically satisfactory.

The Dacron sling technique compares very favourably with the procedures used by other workers (Table 3). Mittleman and Folk[5] in recessing the medial rectus to 13·5 mm from the limbus reduced the angle to less than 15 PD in 18 out of 19 (95%) cases. However, all the patients had esotropias and only one a preoperative angle greater than 40 PD. Of the 18 esotropias in this series 17 (94%) were less than 15 PD postoperatively (the failure being in a sixth nerve palsy), and 10 had a preoperative angle greater than 45 PD.

Table 1 *Surgical details, length of follow-up, and prism cover test results*

Case no.	*Age at surgery (years)*	*Previous surgery*	*Operation*	*Preoperative deviation (prism dioptres)*	*Postoperative deviation (prism dioptres)*	*Follow-up*	*Comments*
*1	12	1 RMR recess. 6 mm, RLR resect. unknown 2 LMR recess. 6 mm, LLR resect. unknown 3 RMR recess. 3 mm on Dacron sling+CR	LMR recess. 3 mm on sling	N 40 ET D 16 ET	N 4 ET D 2 XT	2 months	
*2	21	RMR recess. 3·5 mm, RLR resect. 5 mm	RMR recess. 1 mm+3 mm sling RLR resect. 6 mm	N 45 ET D 50 ET	N 12 ET D 4 ET	4 months	
*3	37	1 RMR recess. 5 mm 2 RLR resect. 10 mm 3 RLR recess. 8 mm	RMR recess. 3 mm on sling RLR advanced 4 mm	N 35 ET D 25 ET	N 10 ET D 4 ET	13 months	
*4	26	Bimedial rectus recess. 4 mm	RMR recess. 2 mm+3 mm sling	N 60 ET D 60 ET	N 14 ET D 14 ET	6 years 4 months	
*5	11	1 Bimedial rectus recess. 5 mm 2 RLR resect. 7 mm 3 LMR myotomy, LLR resect. 8 mm 4 RLR resect. 3 mm	RMR advanced 1 mm+3 mm recess. on sling	N 30 ET D 30 ET	N 18 XT D 14 XT	7 years	
*6	7	1 Bimedial rectus recess. 6 mm 2 LMR recess. 3 mm on sling	LMR recess. 3mm on new sling LLR resect. 5 mm	N 20 ET D 12 ET	N 10 ET D 8 ET	4 years	Sling found surrounded by new tendon
7	8	1 LMR recess. 4 mm, LLR resect. 3 mm 2 RMR recess. 5 mm, RLR resect. 4 mm 3 LMR recess. 3 mm, LLR resect. 5 mm	RMR recess. 3 mm on sling RLR resect. 4 mm	N 53 ET D 45 ET	N 2 ET D 10 XT	3 years	
*8	18	RMR recess. 4 mm, RLR resect. 4 mm	RMR recess. 3 mm on sling RLR resect. 5 mm	N 35 ET D 25 ET	N 8 ET D 8 ET	2 years	Right visual acuity perception of light
*9	4	LMR recess. 5 mm	LMR recess. 3 mm on sling	N 25 ET D —	N 8 XT D —	2 years	Left congenital cataract. Distance result missing
*10	31	1 RMR recess. 9 mm 2 LMR recess. 5 mm, LLR resect. 6 mm 3 RLR resect. unknown	RMR advanced 3 mm+3 mm recess. on sling+CR, RLR resect. 7 mm	N 53 ET D 51 ET	N 16 ET D 6 ET	5 months	
*11	20	LMR recess. 5 mm, LLR resect. 5 mm	LMR recess. 3 mm on sling LLR resect. 4 mm	N 45 ET D 45 ET	N 4 XT D 6 XT	15 months	Left visual acuity perception of light
*12	6	1 LMR recess. 5 mm, LLR resect. 9 mm 2 RMR recess. 5 mm, LLR resect. 9 mm	LMR recess. 3 mm on sling LLR resect. 4 mm LIO+RIO myectomies	N 35 ET D 45 ET	N 14 ET D 14 ET	6 months	
*13	39	Bimedial rectus recess. 6 mm	LMR recess. 3·5 mm on sling LLR resect. 7 mm	N 50 ET D 57 ET	N 4 ET D 10 ET	5 months	
*14	23	Bimedial rectus recess. 5 mm	LMR recess. 3 mm on sling LLR resect. 4 mm	N 35 ET D 25 ET	N 6 ET D 6 ET	2 months	Left visual acuity counting fingers

Case no.	*Age at surgery (years)*	*Previous surgery*	*Operation*	*Preoperative deviation (prism dioptres)*	*Postoperative deviation (prism dioptres)*	*Follow-up*	*Comments*
*15	9	1 RMR recess. 5 mm, RLR resect. 8 mm 2 LMR recess. 5 mm, LLR resect. 7 mm 3 RIO myectomy	RMR recess. 3 mm on sling LMR recess. 3 mm on sling	D 35 ET D 20 ET	N 6 XT D 4 XT	2 years	
16	2	None	RMR recess. 5 mm+3 mm sling RLR resect. 8 mm, RIO myectomy	N 90 ET D —	N 15 XT D—	1 month	Congenital iridocorneal dysgenesis. Too young for distance measurements
17	29	None	LMR recess. 5 mm+3 mm on sling +CR, LLR resect. 9 mm	N 90 ET D 90 ET	N zero D zero	2 months	
18	11	None	LLR recess. 6 mm+3 mm on sling LMR resect. 5 mm	N 70 XT D —	N 12 XT D —	8 months	Left visual acuity PL. Distance result missing
19	33	RMR resect. 6 mm, RLR recess. 8 mm	RLR recess. 3·5 mm on sling RMR resect. 5 mm	N 30 XT D 30 XT	N 40 XT D 35 XT	7 years	Initial improvement. Refused further surgery
*20	28	LMR resect. 5 mm, LLR recess. 6 mm	LLR recess. 3 mm on sling LMR resect. 5 mm	N 65 XT D 50 XT	N 30 XT D 30 XT	1 year	
21	7	1 RMR recess. 5 mm, RLR resect. 5 mm 2 Exploration RLR. Fibrosis to IO. RLR recess. 4 mm 3 RLR fibrosis to IO recess. 4 mm RMR advanced 5 mm	RLR recess. 4 mm on sling LLR recess. 5 mm	N 8 XT D 14 XT	N 4 ET D 6 ET	3 years	Preoperative restriction of right adduction, hence fourth operation
*22	20	LLR recess. 9 mm, LMR resect. 7 mm	LLR recess. 4 mm on sling+CR LMR resect. 5 mm	N 60 XT D 85 XT	N 20 XT D 45 XT	2 months	Left traumatic cataract and densely amblyopic
*23	10	1 Bimedial rectus recess. 2 LMR advanced 3 LMR resect. 2 mm+advanced to 5·5 mm from limbus 4 LLR recess. unknown	LLR found 13 mm from limbus Recess. 3 mm on sling	N 70 XT D 70 XT	N 55 XT D 55 XT	2 months	Further surgery. Left MR resect. 7 mm. LLR explored, sling in situ. Conjunctival recess. Postop. N 6 ET D 4 XT
*24	28	LLR recess. 6 mm, LMR resect. unknown	LLR recess. 3 mm on sling+CR LMR resect. 5 mm	N 45 XT D 35 XT	N 40 XT D 30 XT	6 months	Looks cosmetically better than results suggest
25	24	None	RMR recess. 5 mm+3 mm on sling RLR resect. 10 mm	N 90 ET D 100 ET	N 35 ET D 40 ET	6 months	R VI palsy. Six months later LMR recess. 5 mm+Faden procedure+LLR resect. 7 mm. Postop: N 20 ET D 30 ET
26	7	None	RLR recess. 5 mm+3 mm on sling +CR, RMR resect 6 mm	N 70 XT D 65 XT	N 63 XT D 57 XT	5 years	Congenital III N palsy. Initially good result. Further surgery refused
27	60	None	RMR recess. 5 mm+3 mm sling RLR resect. 10 mm	N 60 ET D 70 ET	N 14 XT N 10 XT	1 month	Bilateral VI N palsy. Diabetic.

Cases. 1–17 esotropias, 18–24 exotropias, 25–27 paralytics.
*Referred from another consultant. Recess.=recession. Resect.=resection. R=right. L=left. N=near. D=distance. MR=medial rectus. LR=lateral rectus. IO=inferior oblique. ET=esotropia. XT=exotropia. PL=perception of light. CR=conjunctival recession.

Table 2 *Degree of postoperative eye movement as measured on synoptophore relating to the muscle having had the sling procedure*

Case no.	*Degree of movement (°)*	*Case no.*	*Degree of movement (°)*
1	L add 29	15	–
2	–	16	–
3	R add 40+	17	–
4	R add 36	18	L abd 36
5	R add 38	19	R abd 32
6	L add 28	20	–
7	R add 32	21	R abd 40+
8	R add 30	22	–
9	–	23	L abd 35
10	R add 38	24	L abd 40
11	–	25	–
12	–	26	R abd 30
13	L add 29	27	–
14	L add 25		

add=Adduction. abd=Abduction.

The postoperative angle is not the sole criterion of successful surgery, as restriction of eye movement may be cosmetically unacceptable. Recessing the muscle to the anatomic equator produces some limitation of movement, and marginal myotomy is said to be superior because it maintains the muscles arc of contact with the eye. Despite these claims, Mittleman and Folk[5] say that 'whatever procedure is performed in a situation where maximal surgery has been carried out, limitation of movement will occur'. When either procedure is combined with a resection, the amount of limitation of movement is increased. Gobin claims that a Dacron sling maintains the muscle's arc of contact with the globe[9] and found that the gap between tendon and insertion became bridged by fibrous tissue by which the tendon became attached to its new insertion. Logically the cut end of the muscle would be expected to become attached posteriorly to the sclera (as is believed to occur in adjustable sutures) and negate the effect of the sling, but in two cases (6 and 23) in which the previous Dacron sling was explored no apparent adhesions were found behind the anterior insertion of the suture. The sling was found to be surrounded by a new tendon of connective tissue, supporting Gobin's experience. To account for these findings we can only suggest that, when the eye is moved into the field of action of the muscle, the cut end is held away from the globe by virtue of its position behind the equator and possibly prevented from adhering to the globe

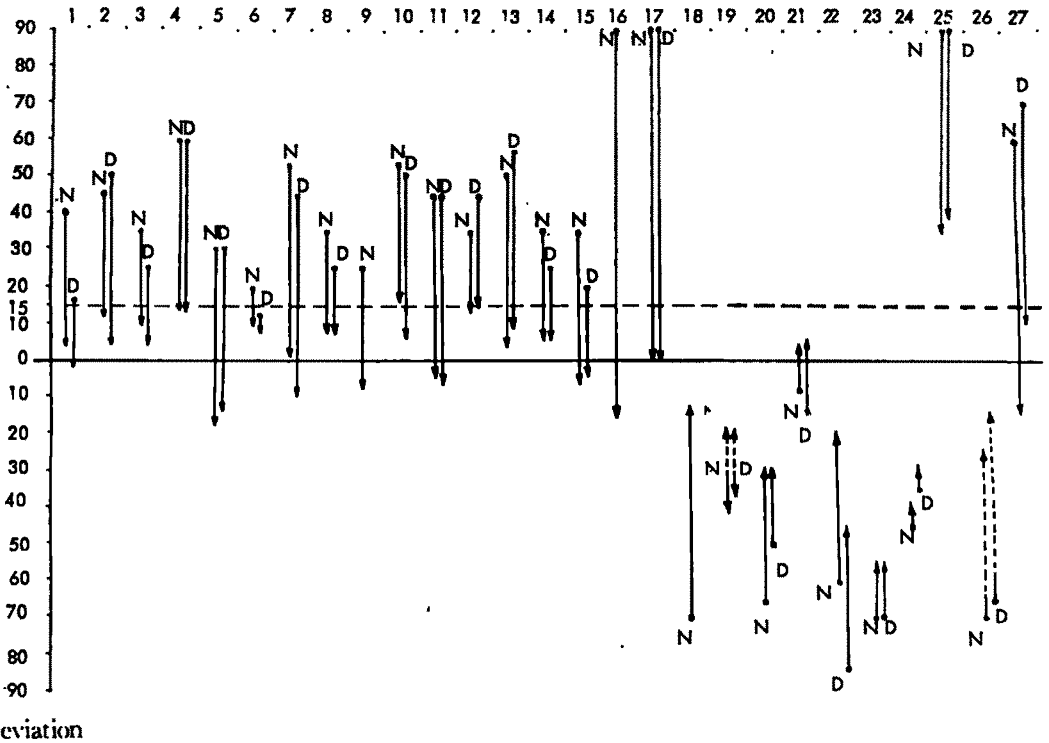

Fig. 2 *Plot of patient versus change in squint angle in prism dioptres (preoperative angle: solid circle, postoperative angle: arrow head; N=near; D=distance; dotted line=initial result).*

Table 3 *A comparison of the various techniques used following previous squint surgery*

Author	*Procedure*	*No. of patients*	*No. of patients with postoperative angle less than 15 prism dioptres*	*Follow-up (average)*
Mittleman *et al.*[5]	Recession to 13·5 mm	19*	18	2 years 3 months
Helveston and Cofield[12]	Marginal myotomy	6†	4	9 months
Nolan[3]	Muscle lengthening	7*	3	10 months
Zak and Morin[14]	Marginal myotomy	5*	1§	7 years
Clark *et al.* (this series)	Dacron sling	21‡	15	1 year 11 months

*All esodeviations.
†Two eso and 4 exodeviations.
‡Fifteen eso and 6 exodeviations (six excluded as no previous surgery).
§Criteria of success less than 10 prism dioptres, as cases were infants.

(Fig. 3). It would be unwise of us to be dogmatic on this issue in view of the limited number of re-explorations (two cases), but whether or not the cut end of the muscle does become reattached posteriorly the postoperative muscle action remained acceptable.

The maximal rotation of the globe is about 50° for both the medial and lateral rectus,[13] and after recession/resection surgery it is usually reduced to 25–30°[5]. In none of the patients in our series was the measurement less than 25°. In 11 cases where the assessment of muscle action on the synoptophore was not possible there was no gross restriction of eye movement. This compares well with Mittleman and Folk's[5] series. Of the six cases reported by Helveston and Cofield[12] two had gross restriction of eye movement (less than 11°), two had 'slight restriction' (no measurement given), and no comment was made on the remaining two. In the series by Nolan[3] information is lacking on this aspect.

It is difficult to quantify the amount the sling procedure contributed to the change of angle following surgery in 21 out of the 27 patients (excluding the paralytics), as all these patients had had previous surgery, and part of the corrective procedure always involved removal of any fibrous tissue and in some cases conjunctival recession. However, in three cases no previous surgery had been undertaken, and in these cases of virginal squints (16, 17, 18) the average correction for distance and near vision for the convergent squints was 90 PD and that for the exotropia (case 18) was 70 PD. The surgeon (RBT) normally expects a maximal recession/resection procedure to achieve 50 PD for near and distance vision for a convergent deviation, and therefore we can assume that the sling contributed to a further 40 PD of correction. Equally for the exotropia this would be expected to correct 45 PD without the sling, and therefore the sling contributed in the region of 25 PD. A muscle lengthening procedure can correct 25–35 PD[3] and recessing to the anatomic equator corrects 20 PD[5] (more if combined with a resection). Thus the sling procedure compares well with these operations.

The operation is safe, as the suturing to the sclera is close to the equator with good visibility, while recession behind the equator, particularly after previous squint surgery, may be extremely difficult. No complications were encountered in any of our cases. It has advantages over other techniques, such as muscle lengthening, because of its simplicity, and it does not restrict the eye movement as much as a myotomy or a recession to the equator, especially

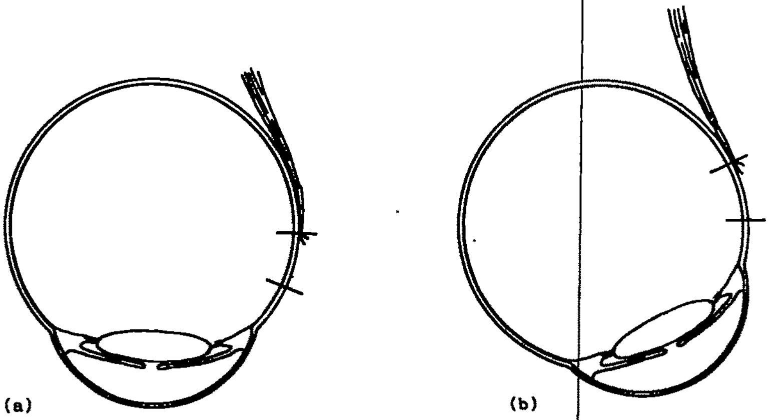

Fig. 3(a) *The eye in the primary position.* (b) *The eye position when the muscle contracts. The cut muscle end is remote from the globe.*

when the latter is combined with a resection. The procedure is also reversible, or secondary loops can be added should any further recession be necessary. However, in our one case (case 6) the effect of the secondary loop was considerably less than the angular correction produced by a primary sling procedure.

CONCLUSION

Twenty-seven patients are reported who had surgery by means of loops to extend the recession of horizontal recti in cases thought unlikely to respond to conventional squint surgery. It is thought that this procedure should be considered for (1) residual squints that have had maximal surgery to both eyes; (2) residual squints that have had maximal surgery on one eye and it is unreasonable to operate on the fellow eye; (3) where an ordinary recession is impossible owing to previous retinal surgery or thin sclera.

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A case of partial 5q trisomy associated with partial 7q monosomy

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SUMMARY A 1-year-old girl with partial 5q trisomy and partial 7q monosomy had ocular abnormalities that included bilateral blepharoptosis and Leber's congenital amaurosis. A single bright-flash electroretinogram (dark-adapted, white stimulation) disclosed subnormal bilateral responses. Her maculas showed a reddish spot surrounded by a broad, greyish retinal zone. Cytogenetic studies disclosed deletion of q22 to the terminal of chromosome 7 and partial trisomy of q31 to the terminal of chromosome 5. Because all reported patients with 5q trisomy have not had Leber's congenital amaurosis, the ocular abnormalities noted in our patient may be explained by the 7q monosomy.

The ability to specify breakpoints and the extent of a deletion have become increasingly reliable with improved techniques that provide elongated chromosomes with detailed banding.[1] Twenty-nine cases of partial deletion of 7q[2-24] and 15 cases of distal trisomy of 5q[25-33] have been reported with corresponding clinical syndromes. Among these, two patients have had intraocular abnormalities, one with unilateral optic nerve coloboma[6] and one with bilateral microphthalmos and a large retinal coloboma.[23] We describe here a patient with partial trisomy of terminal 5q associated a partial monosomy of terminal 7q who had ocular abnormalities, including Leber's congenital amaurosis, and non-specific findings, such as hypertelorism and blepharoptosis.

Case report

A 4-month-old girl was referred to us in August 1982 for bilateral blepharoptosis. The product of a normal, full-term pregnancy, the patient, weighed 2128 g at birth. The Apgar score was 2 at one minute, and supplemental oxygen was administered for one hour. The parents were 35 years old, were not con-

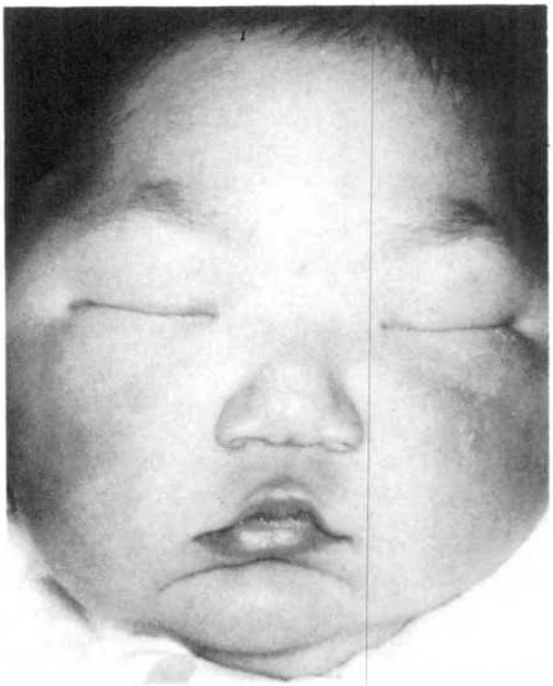

Fig. 1 *Four-month-old girl with telecanthus, broad nose, and microcephaly.*

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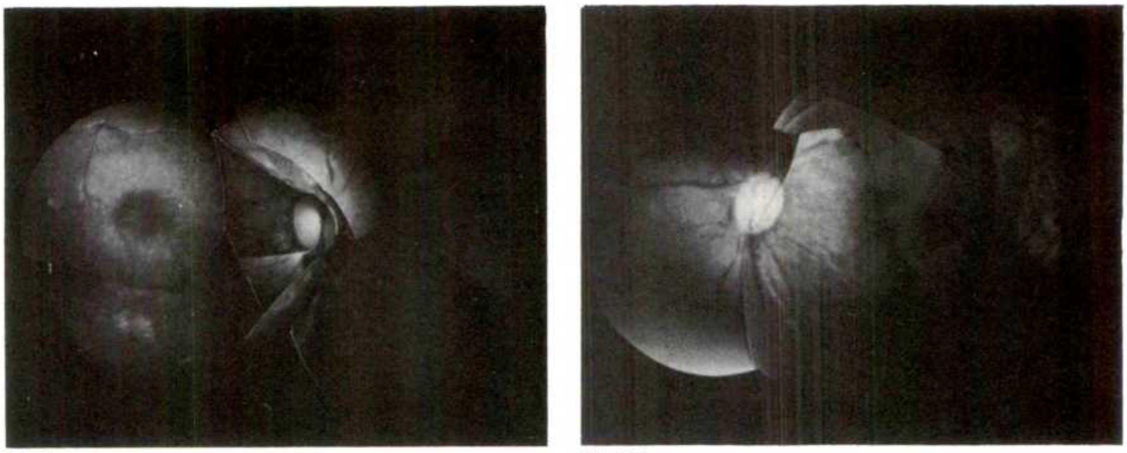

Fig. 2A

Fig. 2B

Fig. 2 A: *right eye.* B: *left eye. The maculas show a reddish spot surrounded by a broad greyish retinal zone. No macular rings are seen.*

sanguinous, and were in good health. A 3-year-old male sibling was normal.

Ocular examination of the patient disclosed bilateral blepharoptosis and telecanthus (Fig. 1). The lid fissure was 3 mm wide in the right eye and 2 mm in the left. The levator function was 0 mm in each eye. A Tensilon test result was negative. Congenital anomalies included microcephaly and a broad nose. Follow-up examination revealed severe mental and physical retardation associated with spastic palsy and hearing impairment. The amino acids in urine and serum were normal. In November 1983 the patient received general anaesthesia to undergo resection of the levator muscle in the right eye through the conjunctiva. Resected material contained no skeletal muscle and only a trace of smooth muscle. The blepharoptosis was not corrected despite a maximal resection.

On the day of the operation additional ocular examinations included electrophysiological studies and fluorescein angiography. The pupillary distance was 50 mm. The anterior segments appeared normal. Ophthalmoscopic examination disclosed no macular rings but showed mottled retina from the posterior to the midperipheral region bilaterally. The maculas showed a reddish spot surrounded by a broad greyish retinal zone (Figs. 2A, B). Fluorescein angiography showed granular hyperfluorescence in the regions that contrasted with the greyish perimacular zones (Fig. 3). A single bright-flash electroretinogram

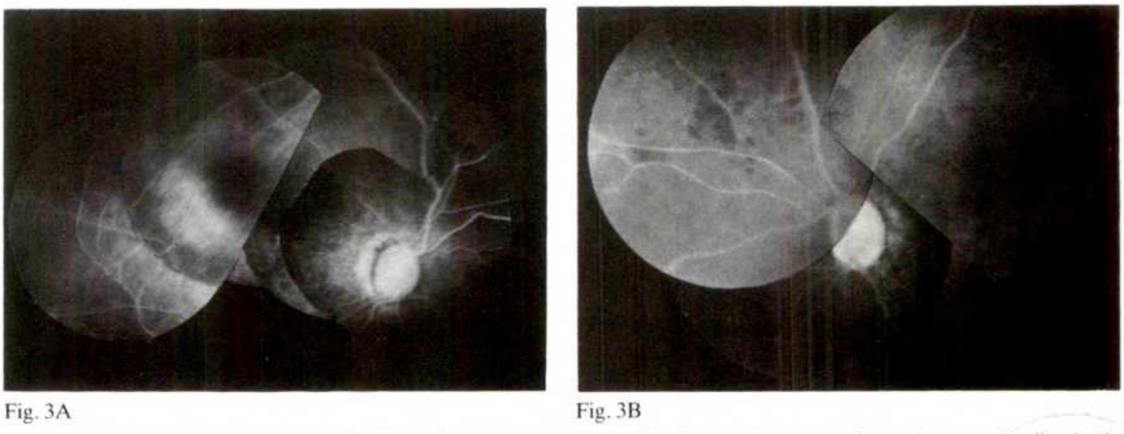

Fig. 3A

Fig. 3B

Fig. 3 A: *right eye.* B: *left eye. Granular hyperfluorescence is observed in the greyish perimacular regions noted in Fig. 2. No leakage of fluorescein is seen.*

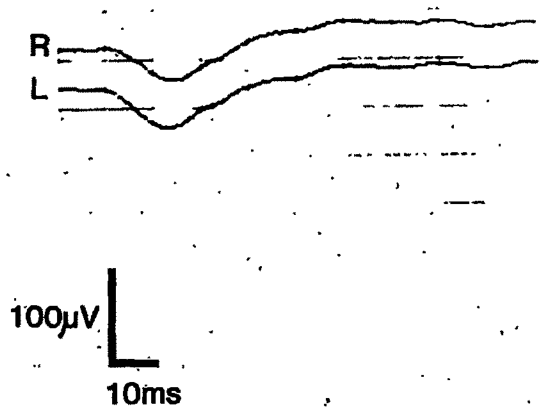

Fig. 4 *Single bright-flash electroretinogram (dark adapted, white stimulation). Both the right* (R) *and left* (L) *eyes show subnormal responses.*

(dark-adapted, white stimulation) disclosed subnormal responses (Fig. 4). Cytogenic studies were performed on peripheral blood lymphocytes. Metaphase chromosomes derived from synchronised cell cultures were treated with trypsin and stained with Giemsa's stain (Fig. 5). The chromosomes showed partial monosomy of the long arm of chromosome 7. The karyotype was 46, XX, −7, +der(7), t(5:7) (q31:q22). A chromosomal study on the mother showed normal findings. The father was unavailable for cytogenic evaluation.

Discussion

Cytogenic analyses have shown a number of cases of chromosomal changes in patients with congenital abnormalities. To our knowledge 15 cases of partial trisomy of the long arm of chromosome 5 have been reported. All such cases proved to be inherited from parental insertion or parental translocation, with breakage of the second chromosome at the terminal band. Under these circumstances various cases of partial monosomy associated with partial 5q trisomy may have gone undetected. Our patient may represent the first case of partial 5q trisomy with partial 7q monosomy, although parental translocation could not be proved because the cytogenic data for the father were incomplete. All previously reported patients with partial 5q trisomy had a low birth weight under 3000 g and physical and mental retardation. Cases of partial trisomy of the distal part of 5q (distal to band 5q31 and to 5q33) commonly had inborn dystrophy and severe to moderate retardation of growth and psychomotor development. Our patient also showed this clinical picture and a breakpoint of 5q31.

The ophthalmoscopic appearance of Leber's congenital amaurosis varies. The most common findings are normal fundus, salt and pepper pigmentary changes, a blond fundus with choroidal atrophy or choroideraemia, classic aspect of retinitis pigmentosa, macular changes, or optic atrophy and narrow vessels.

The electroretinogram diagnostic for Leber's congenital amaurosis is extinguished or shows only minimal response.[34] The parents of our case had subnormal responses to the single white flash in dark-adapted conditions. Also noted ophthalmoscopically were lesions in the posterior pole that included a reddish spot in the macula surrounded by a greyish retinal zone that showed granular hyperfluorescence on fluorescein angiography, indicating Leber's congenital amaurosis.

No intraocular abnormalities have been reported

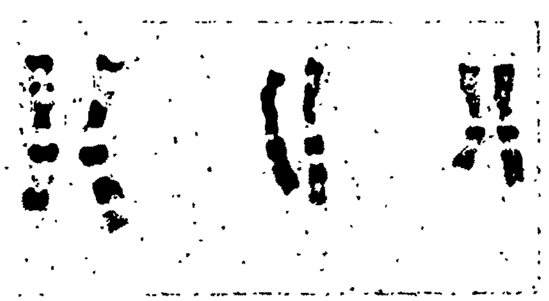

Fig. 5A

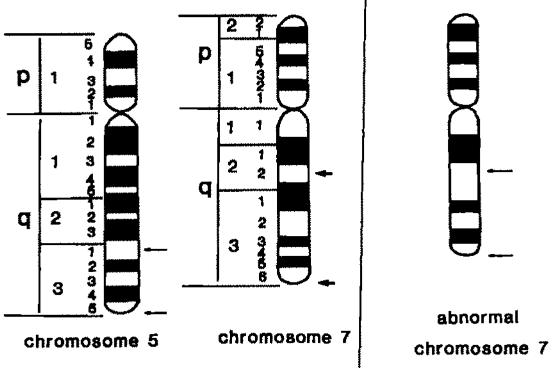

Fig. 5B

Fig. 5 *Partial karyotype of chromosome 7. A: three pairs of metaphase chromosome from patient are demonstrated after trypsin-Geimsa banding. Abnormal chromosome with deletion of 7q at q22 to the terminal is shown to the right of each pair. B: schematic partial karyotype of our patient. One pair of chromosome 5 is normal, and one pair chromosome 7 is abnormal, having a segment of q31 to the terminal of chromosome 5 instead of a segment of q22 to the terminal of chromosome 7. The karyotype is 46, XX, −7, +der(7), t(5:7) (q31:q22).*

previously in cases of 5q trisomy. The ocular abnormalities noted in our patient, compared with other patients with 5q trisomy who had an almost identical duplicated segment, might be explained by the additional monosomy. Chromosome 7q deletion syndrome has included relatively consistent dysmorphic findings, including growth deficiency, developmental delay, bulbous nasal tip, abnormal ears, cleft lip, and genital abnormalities. Acute non-lymphatic leukaemia, secondary to occupational or therapeutic mutagenic exposure, has also been frequently associated with a 7q abnormality.[35] Only two reported cases of 7q deletion syndrome had, however, associated ocular abnormalities. These were microphthalmos and retinal coloboma[23] and a unilateral optic nerve coloboma,[6] though 14 cases of terminal deletion of the long arm of chromosome 7, terminal to q32 and terminal to q35, have been reported. Because there are no reports of the deletion of chromosome 7q22 to the terminal, we cannot conclude that Leber's congenital amaurosis is pathognomonic for 7q deletion syndrome.

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Orbital mucormycosis with survival

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SUMMARY Orbital mucormycosis is reported in a healthy patient with maturity onset diabetes who was treated with orbital exenteration, amphotericin B, and ketoconazole. A six-year follow-up shows no evidence of recurrence.

Orbital mucormycosis is a rare, fatal condition that usually develops in patients with debilitating disease. Reports of the disease in healthy individuals have been few.[1 2] We report only the third surviving patient who developed this condition. In most cases mucor invades tissues that have already been altered by disease.[3] Why a usually saprophytic, non-pathogenic fungus becomes invasive is not clear.

The development of mucormycosis has been attributed to decreased host resistance, local lesions incident to primary disease, and disturbance brought about by therapy. Most cases occur in patients with diabetes. However, other predisposing factors are leukaemia, multiple myelomas, carcinoma, anaemia, burns, septicaemia, and hepatitis. The use of antibiotics, steroids, and ionising radiation favours the growth of the organism.

Diagnosis is often made at necropsy, though some cases are recognised during life. The cerebral form is the most easily identified, since ocular manifestations are apparent in 50% of cases.[4]

Since the introduction of amphotericin B treatment in 1958 several patients with mucormycosis have survived.[5] We report such a patient who is alive six years later and shows no sign of recurrence.

Case report

A 61-year-old Caucasian man presented in July 1978 with a six-week history of double vision. He had diabetes of one year's duration. At examination his visual acuity was 6/6 in both eyes. His right intraocular pressure was 35 mmHg and right proptosis was 21 mm, with loss of right abduction and laevodepression. The fields were full and colour vision was normal, but the thyroxine level was low; however, a TRH–TSH test gave a normal result. A orbital computerised tomography scan was normal (Fig. 1). He was treated with acetazolamide 500 mg twice daily. His proptosis increased to 26 mm over a two-month period and his symptoms remained. He was treated with prednisolone 60 mg daily and given replacement thyroxine. His proptosis reduced to 22 mm and his steroid therapy was tailed off. In February 1979 he returned with proptosis of 25 mm and intraocular pressure of 40 mmHg. Prednisolone 100 mg daily was recommended and his proptosis fell to 23 mm.

In July 1979 he returned with proptosis of 26 mm. Ethmoidal *x*-ray showed thickening and an orbital computerised tomography scan (Fig. 2) confirmed an opaque ethmoidal sinus and an enlarged right medial

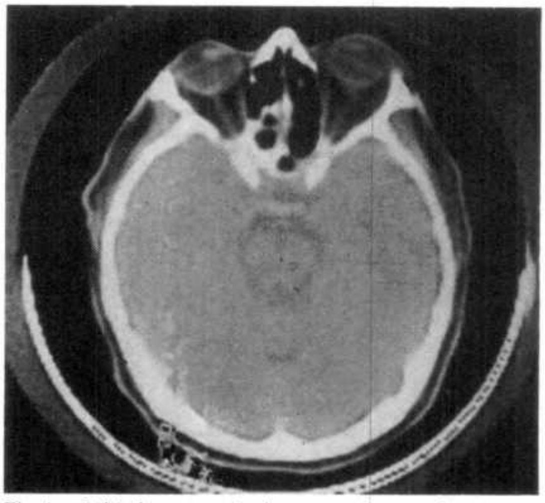

Fig. 1 *Orbital computerised tomography scan showing a normal right orbit and ethmoidal sinus.*

Correspondence to Dr M O'Keefe, Department of Ophthalmology, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8.

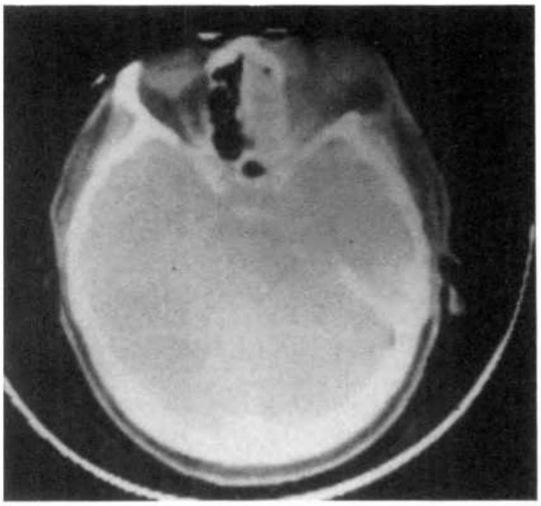

Fig. 2 *Orbital computerised tomography scan showing opaque ethmoidal sinus and thickened medial rectus muscle.*

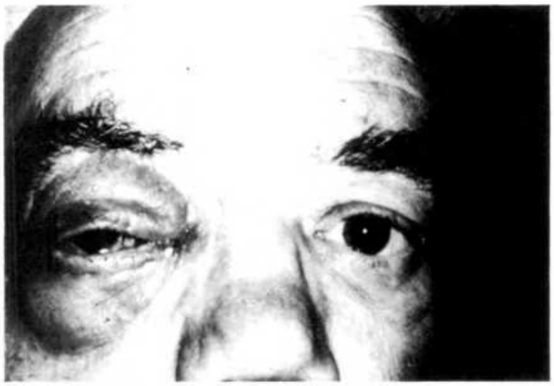

Fig. 3 *Appearance consistent with orbital cellulitis.*

rectus muscle. Subsequently he developed a right ischaemic optic neuropathy and what appeared clinically to be a right orbital cellulitis (Fig. 3). Antibiotics were tried without benefit. He underwent a right orbital and ethmoidal exploration, and cheesy material was removed for biopsy. Culture and histological examination confirmed *Rhizopus* (Fig. 4). He was given amphotericin B intravenously in a dosage of 0·25 mg/kg body weight.

Surgical exploration revealed extensive involvement of the orbit, ethmoidal sinus, and anterior wall and mucosa of the right maxillary antrum. Furthermore, there was fungal invasion in three places in the dura mater of the anterior cranial fossa. With neurosurgical and otolaryngological assistance, orbital exenteration and ethmoidectomy were performed. In addition the orbital floor and antral mucosa were removed. Almost all of the necrotic and infected tissue was excised.

Two weeks after surgery the amphotericin B was stopped and he was started on ketoconazole 200 mg daily for a further six weeks. At four months there was no evidence of recurrence either clinically or radiologically, and he was fitted with an exenteration prosthesis.

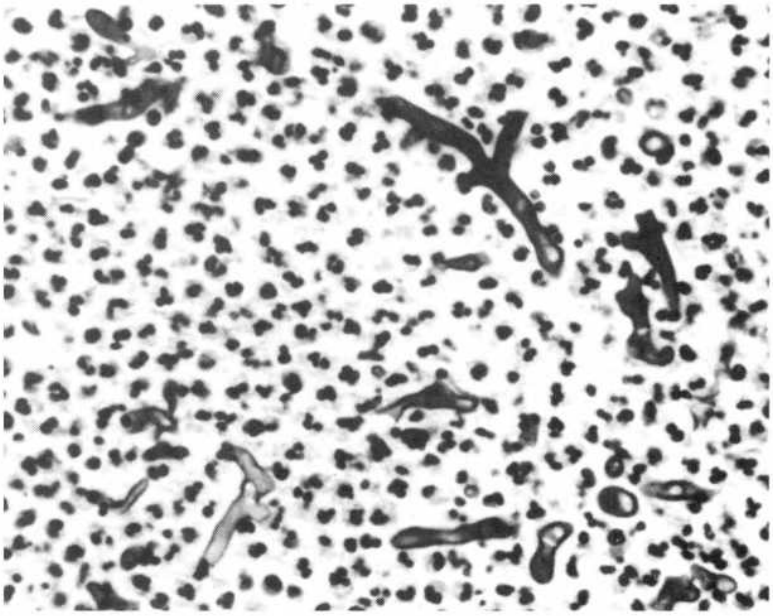

Fig. 4 *Orbital tissue showing typical non-septate hyphae. (H and E, ×300).*

The patient remained well until November 1984, when he presented with a left central retinal vein occlusion. Examination showed no recurrence of *Rhizopus*. Six months later his left visual acuity had not improved beyond 6/60, but he remained well.

Discussion

Although many cases of mucormycosis have been reported, true orbital mucormycosis is very rare.[6] Two cases[7] were reported in patients with poorly controlled diabetes and debilitation who survived. At initial presentation our patient had no evidence of the condition, and the most likely presenting diagnosis was dysthyroid eye disease or orbital pseudotumour. However, the use of steroids and the fact that he was mildly diabetic predisposed him to mucormycosis. The infection started in his ethmoidal sinus and spread directly to the orbit. His case illustrates the preference of this organism to invade blood vessels. He was treated with the antifungal agent ketoconazole[8] because it was considered more effective with fewer side effects than other available drugs; this was the first use of ketoconazole in Great Britain. The drug is now known to cause liver damage in one out of every 15 000 patients treated.[9] However, in the case of our patient the combination of exenteration and antifungal therapy saved his life.

We acknowledge the assistance of Elizabeth Shapter, G Bedford, and Ivan Jacobson.

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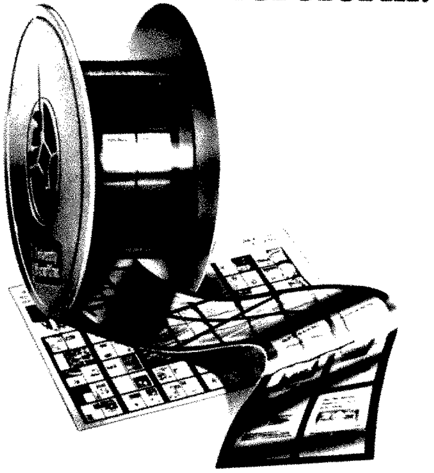

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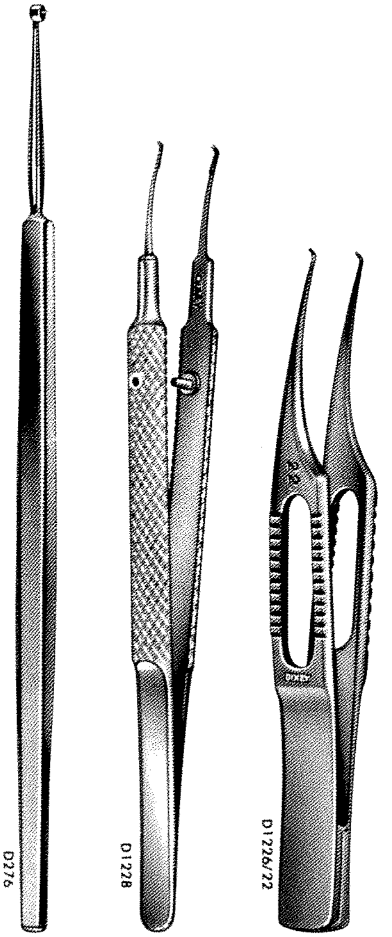

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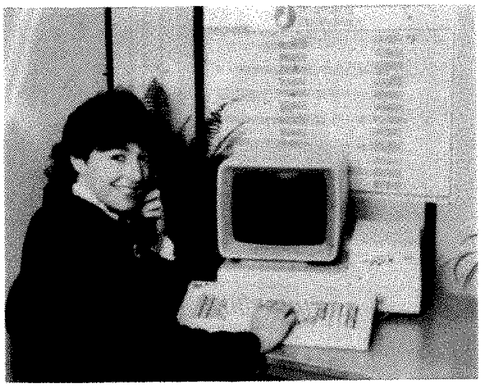

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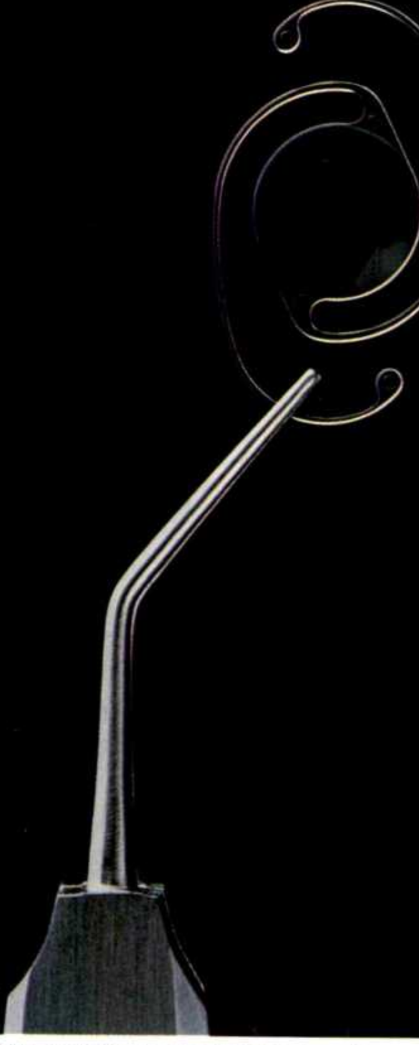

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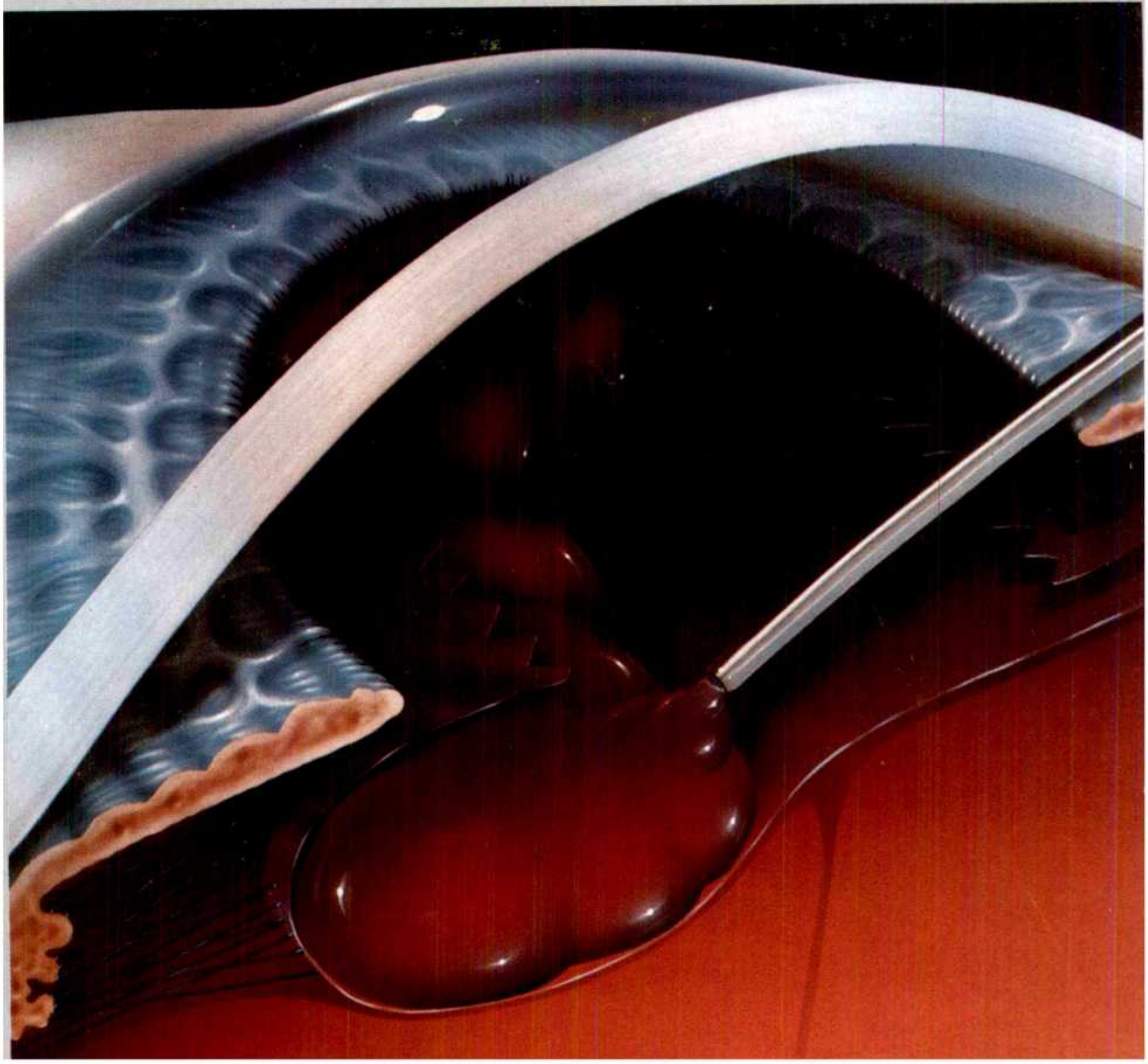

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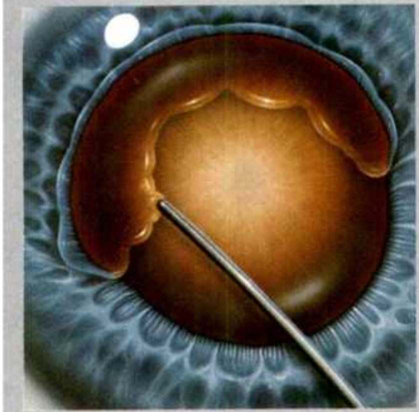

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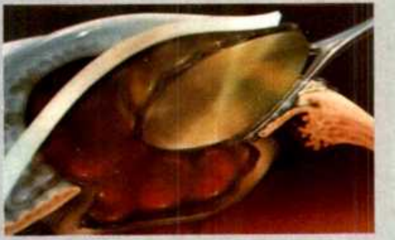

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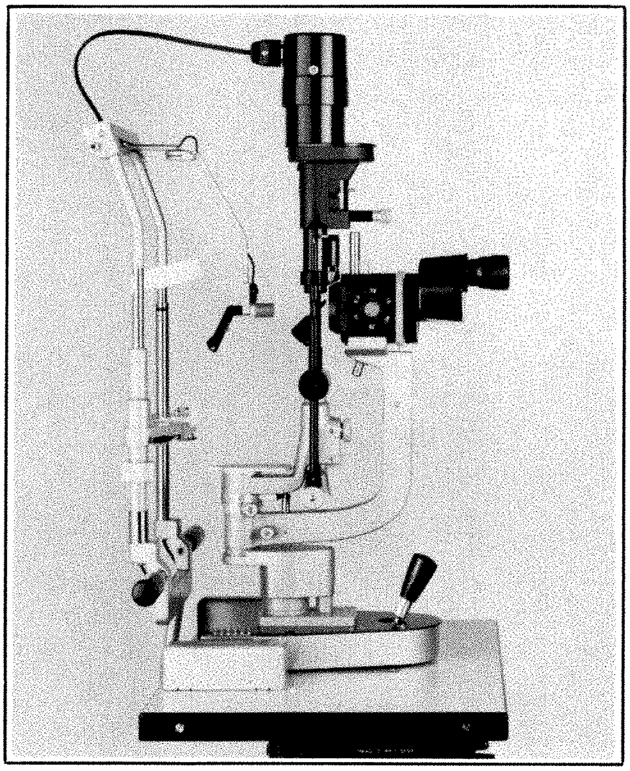

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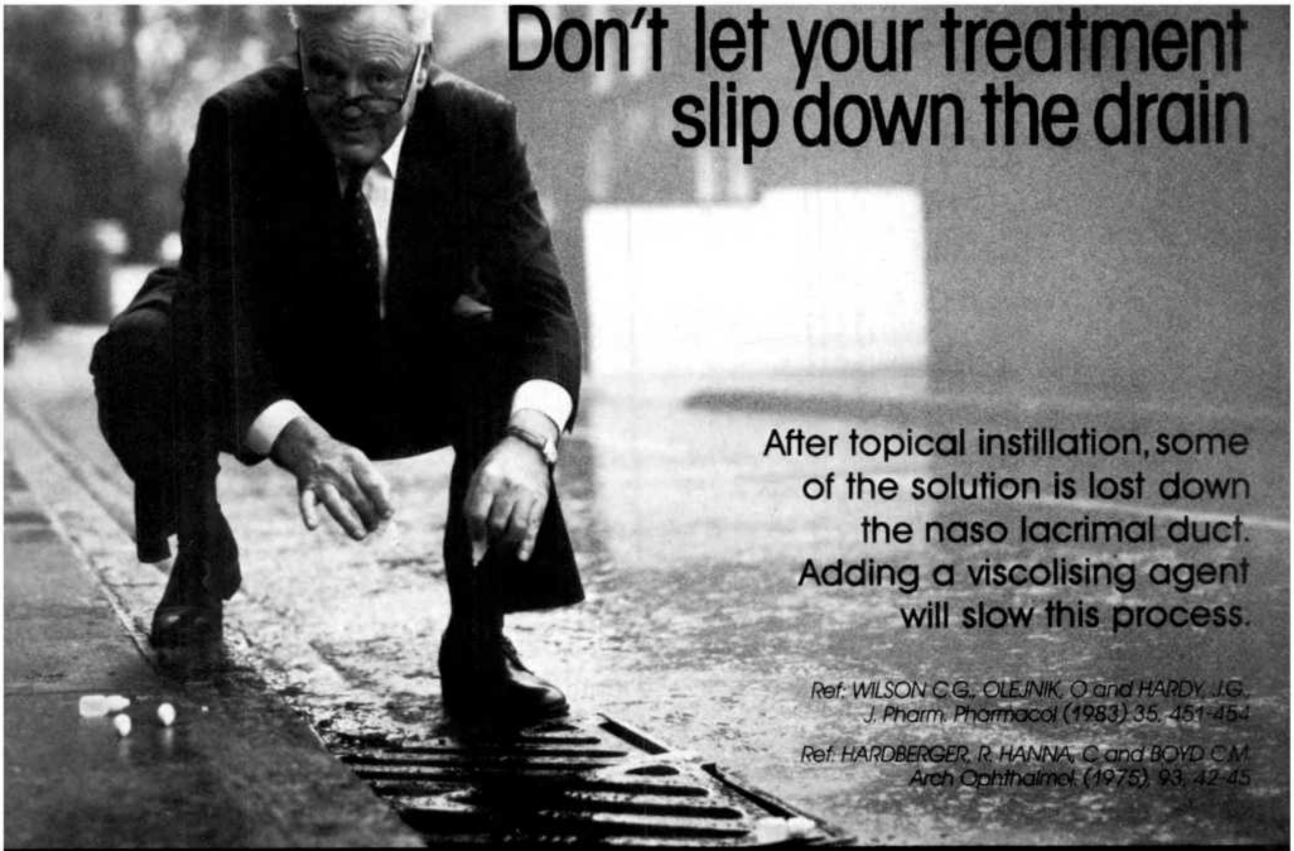

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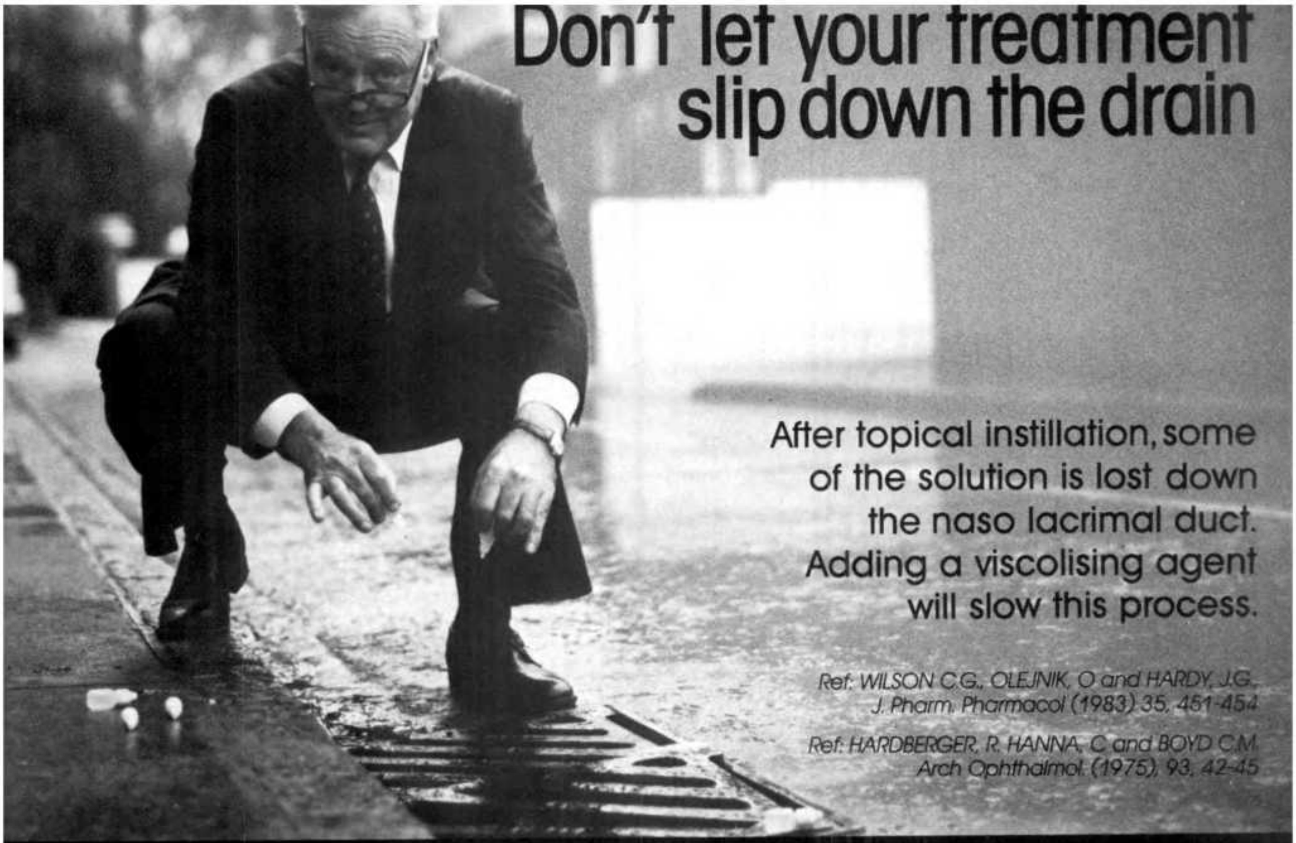

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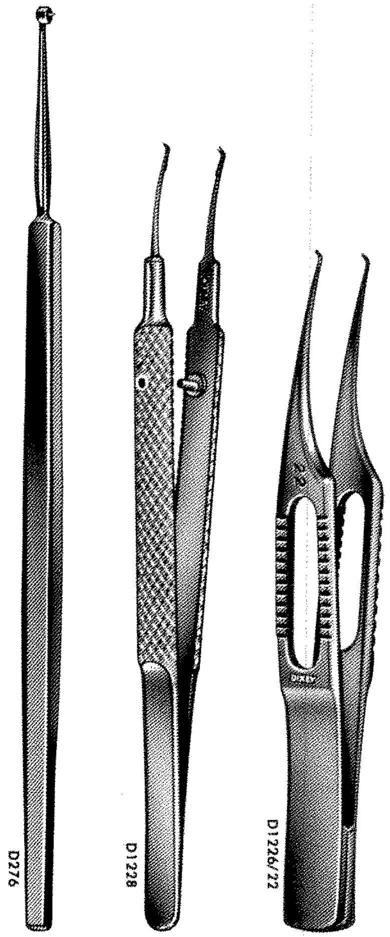

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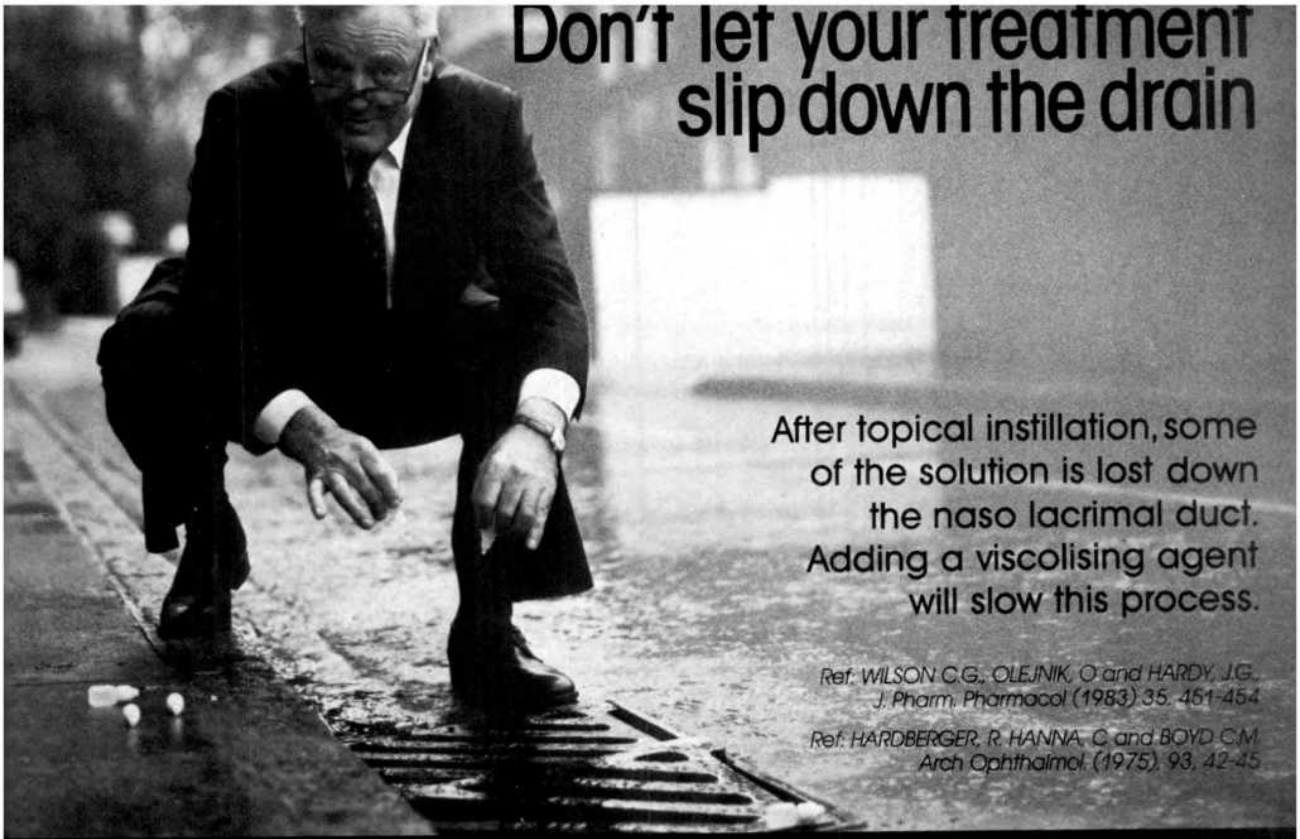

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British Journal of Ophthalmology, 1986, **70**, 637

Editorial: Combined cataract and glaucoma surgery

The presence of both cataract and glaucoma in the same eye has always presented the surgeon with a difficult problem. Very often the cause of the glaucoma is unclear. For example, is the glaucoma in those patients who present with cupping and field loss and very narrow angles the result of a primary narrow angle glaucoma, chronic angle closure from increasing size of the lens, or are the peripheral anterior synechiae and cataract the result of low grade intraocular inflammation? Even those patients who are known to have primary open angle glaucoma which has been controlled with medication do not present a homogeneous group, for many have rigid and unreactive pupils and many have gross abnormalities in the trabecular meshwork; in addition is that curious group of patients who develop an intractable glaucoma after cataract operations. Thus, although there is now a large literature covering the combination of cataract and glaucoma, the best method of management is still in doubt for the individual patient. The decision as to the correct method of treatment depends on a careful preoperative assessment of the nature of the glaucoma and the adequacy of its control. Several alternatives are possible: to control the intraocular pressure medically and remove the cataract intra or extracapsularly; to control the glaucoma surgically and remove the cataract by either method; to combine the procedures for the glaucoma and the cataract; and finally to do any of the above operations with the introduction of an intraocular lens.

Simply removing the cataract rarely has a lasting effect in controlling the glaucoma. Glaucoma surgery in aphakic eyes is less successful than in phakic eyes, and success is dependent on a total absence of complications, because the prognosis becomes very poor if there is vitreous loss, vitreous plugging of a previous filtering procedure, or an excess of soft lens matter plugging an already compromised angle. Pretreatment of the glaucoma by filtering surgery is much more successful and very safe, but a fair proportion of blebs fail to function after cataract surgery. The combined operation of cataract extraction and trabeculectomy is successful but is often followed by a shallowing of the anterior chamber. For this reason anterior chamber and pupil supported intraocular lenses with the optic in front of the pupil are regarded as contraindicated, because corneal contact is almost inevitable. Implantation of posterior chamber intraocular lenses of the pupil supported type described in the article in this issue are very satisfactory in that they tend to draw the lens/iris diaphragm backwards and, particularly with the use of pilocarpine, will open the trabecular pores (if any normal function remains). However, the rigid pupil presents problems which make not only the cataract extraction more difficult but the chances of lens dislocation high. Extracapsular cataract extraction and posterior chamber lens with filtering surgery are also possible, but the difficulties of performing a perfect extracapsular extraction with a possibly poorly dilating pupil are considerable.

Techniques change fast, so fast that well controlled studies have become impossible, so it will probably be some time before we have the perfect answer to this difficult problem.

PGW

British Journal of Ophthalmology, 1986, **70**, 638–641

Combined intracapsular cataract extraction and trabeculectomy with Severin five-loop posterior chamber intraocular lens*

J A COLEIRO

From the Department of Ophthalmology, Ninewells Hospital and Medical School, Dundee

SUMMARY The efficacy and safety of a combined operation for cataract and glaucoma is established. This procedure of combined cataract extraction and trabeculectomy is taken one step further by the simultaneous insertion of the Severin intraocular posterior chamber lens implant. The results of treating 24 eyes in terms of control of glaucoma are discussed. Postoperative miotics may be required to improve stability of the implant, especially after delivery of the lens through a pupil rendered tight by long term preoperative miotic administration.

The association of cataract and glaucoma is a common problem in clinical practice. Attitudes differ on the management when lens opacities justify cataract surgery. The traditional approach has been to carry out filtering surgery followed by intracapsular lens extraction at some future date.[1] With the universal adoption of trabeculectomy[2,3] as the drainage procedure of choice, several studies have confirmed the safety and good results of this procedure when combined with intracapsular cataract extraction.[4-12]

The universal difficulty has been to reconcile the desire for a secure cataract wound and at the same time obtain a filtering effect without the risk of a flat anterior chamber in the early postoperative period. Owing to the encouraging results of an earlier study without implantation,[10] the procedure has been taken one step further by the insertion of a posterior chamber implant.

Materials and methods

Twenty-two patients (24 eyes) with open-angle glaucoma of a known duration of 2–20 years were admitted for cataract surgery between 1980 and 1984. Seven were males and 15 were females of an elderly age group (56–94 years; mean age 78 years). Two patients had bilateral procedures.

The glaucoma was controlled preoperatively by timolol alone in six eyes, with a mean reading of 18 mmHg, by several preparations in nine other eyes, and with additional oral carbonic anhydrase inhibitors in a further five. Four eyes were uncontrolled on maximal medical therapy. Four eyes had previous filtering surgery, two of which were uncontrolled.

The implant power was determined by keratometry and axisonics biometry. Implant powers used ranged from 16 D to 24 D, with the 21 D lens used in 70% of cases.

SURGICAL TECHNIQUES (Fig. 1)

General anaesthesia was employed for operations on 21 eyes, with the remaining three being carried out under local anaesthesia.

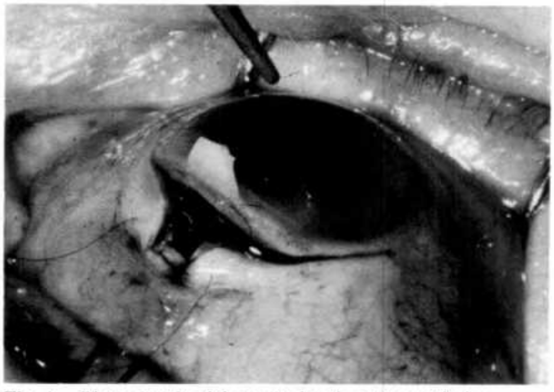

Fig. 1 *Photograph of the completed section with the trabeculectomy and iridectomy.*

---

*Presented to the Third Congress of the European Intraocular Implantlens Council, Harrogate, 11–14 September 1984.

Correspondence to Dr J A Coleiro, FRCS, Department of Ophthalmology, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland.

A fornix based conjunctival flap is reflected at the superior limbus. The underlying sclera at the limbus is lightly touched with bipolar diathermy to check bleeding points, mapping out the proposed region for the trabeculectomy. A 3×2·5 mm half-thickness limbus-based scleral flap is fashioned by a diamond knife tapering slightly towards the cornea and reflected forwards. Prior to completing the trabeculectomy a corneoscleral groove is prepared. After completion of the excision of a 2×2 mm inner corneoscleral lamellar flap by Vannas scissors the cataract incision is extended on both sides by inserting Troutman scissors through the trabeculectomy opening. A peripheral iridectomy is performed. Posterior synechiae from previous surgery or prolonged miotic therapy are gently divided. Several 10/0 monofilament black nylon sutures are prepared, with a loop in the 12 o'clock position of the trabeculectomy flap to enable the assistant to open the wound without damaging the scleral edges. The lens is delivered by cryoextraction. Miochol (acetylcholine chloride 1%, mannitol 3%) is irrigated into the anterior chamber to produce miosis, followed by an air bubble.

A Severin five-loop lens implant (Iolab) is inserted into the posterior chamber by Clayman's forceps. The anterior superior loop of the implant is then anchored to the iris close to the iridectomy by transfixing with 10/0 monofilament nylon.

The preplaced nylon sutures are locked tightly, with the least stable part of the incision on either side of the trabeculectomy flap secured by deep oblique sutures. The scleral flap is also sutured firmly with about five knots. All nylon ends are reversed and buried.

Air is aspirated from the anterior chamber and replaced by more Miochol or balanced salt solution (Alcon). The conjunctival flap is pulled down over the incision and sutured at either end by 8/0 Dexon. A subconjunctival injection of 20 mg Depo-Medrone (methylprednisolone acetate) is given into the lower fornix.

Postoperative miotics and topical steroid drops are administered for several weeks; the former are slowly withdrawn once implant stability is apparent.

COMPLICATIONS

Intraoperative. A ruptured capsule occurred in one eye; all cortical and capsular material was evacuated. Vitreous was lost on one occasion and the wound and anterior chamber were cleared by a Kaufman vitrector unit.

Some difficulty was encountered with pupillary dilatation in four patients on previous miotic therapy or surgical adhesions. Extraction of the cataract stretched the pupil which was reluctant to constrict fully to a hexagonal shape characteristic of a Severin implant, in spite of intracameral irrigation with Miochol.

Postoperative. Three patients had a shallow anterior chamber in the early postoperative period; in one instance choroidal detachments were observed. All settled by firm bandaging and oral acetazolamide without resort to inflating the anterior chamber. None resulted in loop contact with the cornea or evidence of any effect on the endothelium.

Two patients had a small hyphaema at the first dressing which cleared in three days. Four patients have a permanently semidilated 4 mm pupil resulting from sphincter damage by the lens delivery through a tight pupil, in spite of long-term postoperative miotics (pilocarpine 4%). None of these implants have become dislocated, but this is possible should dilatation of the pupil become necessary for examination of the peripheral retina. Two eyes show a small amount of vitreous emerging between the implant loops into the anterior chamber. Cystoid macular oedema has not been observed in these eyes or the rest of this series.

The majority of operated eyes showed no significant degree of postoperative inflammation; the topical steroid drops were withdrawn altogether after six weeks. One eye developed a late inflammation of the implant (15 months) with large cellular precipitates adherent to both surfaces of the intraocular lens. These responded rapidly to a further subconjunctival depot steroid injection, with their complete dissolution within two weeks. The precipitates on the posterior surface were absorbed later than those situated anteriorly.

There was no case of pupillary blockage.

Results

Effects on intraocular pressure. There was an early pressure rise above 24 mmHg in six eyes (25%), but this settled within a few weeks or months. This may have been steroid-related.

The intraocular pressure was assessed at six and at 12 months (mean 15·7 mmHg) and the procedure determined as successful if the reading was 20 mmHg or less. Twelve eyes (50%) were controlled off all treatment, with five eyes (20·8%) on pilocarpine. Three eyes (12·5%) required pilocarpine and timolol, with another three eyes controlled on timolol only. The glaucoma was uncontrolled in one eye (4·1%), which still requires multiple preparations.

Follow-up ranged from 12 months to five years. It appeared that, if the pressure was controlled at six months after operation, subsequent follow-up showed this to be retained.

Filtering blebs. Evidence of filtration was observed in 15 eyes (62·5%), most showing a very shallow and diffuse bleb. No late bleb was present in nine eyes (37·5%). Five eyes with no bleb were controlled without therapy.

Visual results. Eighteen eyes (75%) achieved a corrected acuity of 6/12 or better. Four eyes (16·6%) had significant recovery of useful vision in the range 6/18 to 6/60 due to various grades of senile macular degeneration. Two eyes (8·3%) had a postoperative vision of less than 6/60 due to advanced senile macular disease and gross glaucomatous optic nerve damage.

The degree of astigmatism was less than 2 dioptres in all cases. The visual fields showed no deterioration.

Discussion

Should surgical management of both cataract and glaucoma be indicated, there are several options available. The glaucoma procedure may be performed before, after, or at the time of lens extraction. Prior glaucoma surgery may require the surgeon to modify the standard cataract incision by making a lateral or even an inferior incision. Inflammation and healing may possibly occlude a functioning bleb.

Simple cataract surgery alone can have a pressure lowering effect, but this is often only temporary.[4]

Combined procedures for glaucoma and cataract are currently being adopted as standard ophthalmological practice. The presence of an intraocular lens puts inevitable restrictions on medical therapy and any eventual glaucoma surgery. Most surgeons have therefore been reluctant to undertake the insertion of a lens implant at the same time as a combined operation. Some would even regard pre-existing glaucoma as a relative contraindication to intraocular lens surgery.[13] Prepupillary iridocapsular lens implantation has been undertaken after fistulising surgery by Binkhorst and Huber[14] on eyes which had a functioning filtering bleb and normal levels of intraocular pressure. Amar[15] carried out posterior chamber lens implantation with intracapsular cataract extraction three months after Lagrange sclerectomy, using a corneal section.

In recent years extracapsular cataract techniques have been used more often. Praeger found no appreciable difference between intracapsular and extracapsular removal of the cataract in terms of visual result or glaucoma control,[12] Binkhorst and Huber[14] found though an extracapsular technique to be more satisfactory.

An angle-supported Kelman anterior chamber lens has been proposed by Stiegler[16] as being indicated for use with a combined procedure with the trabeculectomy sited at 10 or 2 o'clock, and he suggests that iris supported lenses of the Binkhorst type are contraindicated. Rigid anterior chamber lenses such as the Choyce Mk IX also have a place in combination with trabeculectomy,[17] though in the long term elliptical pupils have been frequently observed. This lens can also be implanted in combination with cataract extraction in an eye which had a previous trabeculectomy.

A pupil supported lens of the Severin type is not recommended if the pupil is not capable of satisfactory constriction; an anterior chamber lens is to be preferred in this instance.

Montgomery and Gills[18] have combined Shearing lens insertion with cyclodialysis with satisfactory results. Since this procedure does not depend on the pupillary sphincter for fixation and centration, the ruptured sphincter is less significant.

The additional surgical manoeuvres involved in the insertion of the Severin implant do not increase operative morbidity. Tight wound closure is essential for the prevention of a flat anterior chamber. The optical result is superior to that given by aphakic spectacles in the presence of glaucomatous field defects.

Phakic trabeculectomy has a long-term success rate of at least 75% in most series. This rate is reduced by simultaneous cataract extraction, and reduced further to about 50% if the procedure is extended to include lens implantation.[10 17]

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Herpes simplex virus type 1 persistence and latency in cultured rabbit corneal epithelial cells, keratocytes, and endothelial cells

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SUMMARY Cell cultures of rabbit corneal epithelium, keratocytes, and endothelium were used to determine the lytic cycle of herpes simplex virus type 1. Viral growth was fastest in epithelial cells. A novel HSV-1 in-vitro latency system was established in the three distinct cell types. Cell cultures were inoculated at low multiplicities of infection with HSV-1. Temperature manipulation alone was used to induce and reactivate latent HSV-1 infections. The presence of cellular stress proteins was demonstrated at supraoptimal temperatures. All cell types were capable of maintaining latent viral infections under these conditions. Viral persistence was present in 20% of epithelial cell cultures at supraoptimal temperatures, but not in keratocyte cultures or endothelial cell cultures.

Herpes simplex virus (HSV) can react with host cells in vivo or in vitro to produce cytocidal infection, persistent infection, transformation of cells, or latent infection. Latent HSV appears to reside preferentially in the neurones of the dorsal root ganglia and the virus has been isolated from human ganglion explants[1 2] and animal ganglion explants.[3-5]

The possibility that peripheral non-neural sites may support a persistent or latent HSV infection has been suggested by the isolation of virus from the clinically normal skin of latently infected mice,[6] by the isolation of virus from guinea-pig skin when virus was not found in the corresponding ganglia,[7] and by the isolation of virus from the footpad of mice.[8] HSV has also been isolated from ocular explants after long periods of cocultivation.[9]

Latent virus can reactivate in vivo to cause viral shedding with no evidence of clinical disease in rabbit eyes,[10] or it can produce recrudescent epithelial disease in mice.[11] In man ocular herpes simplex virus infection may affect the cornea and cause significant morbidity. Recurrent disease can cause progressive opacification and scarring of the cornea resulting in visual impairment and blindness. The disease is initially superficial, affecting epithelial cells.[12] However, severe disease can involve the deeper stromal layers, affecting the keratocyes.[13] Corneal endothelial cell involvement has also been demonstrated.[14]

Previous studies on fixed human corneae have demonstrated viral particles by electron microscopy[15 16] or the presence of viral antigens by immunofluorescence.[17] However, recovery of infectious virus from deeper corneal layers during quiescent periods has been largely unsuccessful. Recent reports[18 19] have shown that virus was recovered from six out of nine corneae removed in the course of treatment for chronic stromal keratitis. Virus was isolated from the explanted corneae after five to 11 days in culture.

Three possibilities exist:[19] virus is truly latent in corneal cells; virus persists within corneal tissue as a chronic low grade infection; or, prior to explantation of the cornea, the virus is transported to corneal cells from another source, namely the trigeminal ganglion.

In-vitro models of latency have been used in an attempt to elucidate the mechanisms of HSV latency. A number of cell systems have been utilised, including HEL fibroblast cells,[20] rat fetal neurones,[21] human fetal neurones,[22] and transformed neuroblastoma cells.[23] A latent viral state can be induced in infected cells by antiviral agents with,[24] or without,[20] interferon and maintained by temperature elevation.[25] A raised temperature alone has been shown to induce a latent viral state in HEL fibroblast cells in vitro.[26] Temperature elevation induces the production of

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cellular stress proteins.[27] The synthesis of these proteins can also be induced by HSV itself, though the presence of the proteins is transient in a lytic viral infection.[28] The induction of cellular stress proteins by virus may have a role in the induction and maintenance of HSV latency. The factors controlling viral latency are unknown. Reactivation of infectious virus can be achieved in vitro by manipulation of the physical or chemical environment and by viral superinfection.[24 29]

The cornea contains three different cell types: epithelial cells, which replicate throughout life; keratocytes, which tend to be stable but have the potential for replication; and endothelial cells, which do not divide in vivo.[30 31] The aims of the present study were to determine whether the three rabbit corneal cell types could support lytic HSV-1 infection; whether these cells were capable of supporting latent HSV-1 infection; and whether there was a difference in the ability of the epithelial cells, keratocytes, and endothelial cells to support latent HSV-1 infection. It seemed pertinent to develop an in vitro latency system using cells in which the virus is known to occur in vivo, as a first step towards understanding the nature of the virus cell relationship in herpetic keratitis.

Material and methods

GROWTH OF VIRUSES

Virus stocks were grown and titrated in baby hamster kidney cells (BHK21C13) cultured in Eagle's medium (Glasgow modification) plus 10% (v/v) calf serum (EC10). The virus strain used was HSV-1 Glasgow 17.[32]

CELLS

Rabbit corneal cells were prepared by the method of Stocker *et al.*[33] The corneae of New Zealand white rabbits (Hyline Rabbit Farms) were prepared by microdissection. Primary cultures of endothelial cells were obtained by separating Descemet's membrane from the stroma. The membrane was placed in tissue culture flasks (Nunclon 25 cm^2) in growth medium which allowed the endothelial cells to migrate and proliferate. Epithelial cells were separated from the stroma by dissection and grown in flasks separately from the keratocytes, which migrated slowly from within the stroma before proliferating. Secondary cultures were obtained by splitting confluent primary cultures 1:2 with trypsin/versene. The medium found to give optimal growth of the three cell types was as follows: epithelial cells, Eagle's medium (Glasgow modification) plus 10% (v/v) fetal calf serum; keratocytes and endothelial cells, 20 mM Hepes buffered Dulbecco's medium plus 10 (v/v) fetal calf serum, supplemented with 1% (v/v) L-glutamine. Cultures were grown at 37°C.

ONE-STEP GROWTH EXPERIMENTS

Confluent 35 mm plates of BHK 21 C13 cells (10^5 cells), corneal epithelial cells (10^5 cells), keratocytes (10^5 cells), and endothelial cells (5×10^4) cells were infected with HSV-1 Glasgow 17 strain at a multiplicity of infection (MOI) of 10 plaque-forming units (PFU)/cell. After absorption for 1 hour at 37°C the cultures were washed twice in phosphate buffered saline (PBS) plus 5% (v/v) calf serum (PBSC5) and overlaid with EC10. At various time intervals between 0 and 24 hours the infected cells were harvested and virus released by sonication. Samples were stored at −70°C and virus titres measured by plaque assay on BHK 21 C13 cells.

NON-PRODUCTIVE INFECTIONS IN CORNEAL CELLS

Twenty-four confluent cultures of each cell type were grown in 25 cm^2 flasks (approximately 10^6 cells/flask) at 37°C. The cells ranged from pass nos. 5–8 (epithelium); pass nos. 12 (keratocytes); or pass nos. 5–8 (endothelium). Cultures were maintained at 41·5°C for 24 hours prior to HSV-1 infection.

Eight flasks of each of the three corneal cell types were inoculated at MOIs of 0·01, 0·1, and 1·0 PFU/cell in 100 µl of medium. Virus was absorbed for 45 minutes at 41·5°C. The cultures were then overlaid with the appropriate medium, which was changed every third day.

The presence of infectious virus was determined by two methods: (1) observation of viral plaque on the corneal cell cultures; (2) assay of 0·5 ml corneal cell culture supernatant on BHK 21 C13 cells. The assays were performed daily for two days after inoculation and then every third day, when the medium was changed.

At weekly intervals after inoculation two cell cultures at each MOI and of each cell type were transferred to 37°C The medium was supplemented with 5% (v/v) human serum (HS) for the first five days at 37°C. Human serum was added to neutralise any residual extracellular virus.

PREPARATION OF CORNEAL CELL PROTEIN GELS

Radiolabelling of cells. Growth medium was removed from confluent 35 mm plates of epithelial and keratocyte cells and the cellular monolayers washed twice with PBS. Methionine-free Eagle's medium plus 2% (v/v) calf serum was added. After 4 hours 10 µCi of ^{35}S methionine was added to each culture for a further two hours. Control cultures infected with HSV at an MOI of 20 PFU/cell were labelled with ^{35}S methionine for 24 hours. After incubation, labelling medium was removed, monolayers were washed with ice cold PBS and cells disrupted in electrophoresis sample buffer.

Polyacrylamide gel electrophoresis. Radiolabelled samples were analysed by sodium dodecyl sulphate (SDS)—plyacrylamide gel electrophoresis using 7·5% gels.

Gels were dried and autoradiographs prepared.[34]

Results

CHARACTERISATION OF CORNEAL EPITHELIAL, KERATOCYTE, AND ENDOTHELIAL CELLS

The purity of the three distinct corneal cell types was established by indirect immunofluorescence with antibodies against fibronectin which identified the fibroblast-like keratocyte cells[35] and endothelial cells;[36] and by indirect innumofluorescence with antibodies against keratin which identified epithelial cells.[37] Additional electron microscopy studies demonstrated distinct morphological characteristics of the three cell types, which permitted identification (manuscript in preparation).

ONE-STEP GROWTH KINETICS OF HSV-1 IN THREE CORNEAL CELL TYPES

To determine whether the three corneal cell types could support normal HSV-1 lytic growth, single-cycle growth experiments were carried out in epithelial cells, keratocytes, and endothelial cells with BHK 21 C13 cells as control cultures. The experiment was done in duplicate, and the results are presented in Fig. 1 (a-d).

The results show that HSV-1 Glasgow strain 17 could replicate efficiently in the three corneal cell types. Distinct differences were observed. The curve for viral growth in BHK 21 C13 cells characteristically showed a four-hour eclipse phase, a plateau of virus production within 24 hours, and a viral yield of around 100 PFU per cell (Fig. la). The viral growth curve in epithelial cells was similar, but the eclipse phase was slightly prolonged to six hours (Fig. 1b) Virus growth in keratocyte and endothelial cells showed a markedly prolonged eclipse phase of eight hours. The rate of growth was slower in both keratocytes and endothelial cells. Both curves were still in the logarithmic phase at 24 hours, suggesting that virus production had not reached a maximum by that time (Fig. 1c and d).

NON-PRODUCTIVE INFECTIONS IN CORNEAL CELLS.

It has been suggested that the cornea may be a site of latent/persistent HSV infection.[19] One way of determining which, if any, of the corneal cell types are capable of harbouring HSV in a non-infectious form is to induce conditions under which corneal cells are either unable to support, or able to suppress, virus replication. This was achieved by infecting the three types of corneal cells with HSV-1 at various low multiplicities of infection at 41·5°C. Supraoptimal temperatures are known to induce the production of heat shock polypeptides.[26 28 38] The cultures at 41·5°C were monitored for infectious virus for up to 28 days after inoculation. At weekly time intervals during the 28 days cultures were transferred to 37°C and monitored for the shedding of infectious virus. Two assay methods (see 'Materials and Methods') were used to determine the presence of infectious virus. There was 87%, 79%, and 77% correlation between the two assay methods in the epithelial, keratocyte, and endothelial cells respectively. The results presented are from the corneal cell culture supernatant assay on BHK 21 C13 cells.

At the start of the experiment there were 24 cultures of each cell type. Cells were able to divide at 41·5°C, so when cells became overconfluent, the cultures were split 1:2. The progeny cultures continued in the experiment at 41·5°C, increasing the original number of cultures (Table 1, a-c, column 1)

Infectious virus was detectable in all cultures on the first day after inoculation and in most cultures on the second day after inoculation (data not shown). A focal cytopathic effect, observed by rounding of cells, was seen to some extent in all cultures after HSV-1 infection. At higher MOIs (0·1 and 1·0 PFU/cell) cell death could be overwhelming by the seventh day, leaving no surviving cells. This was marked in keratocyte and endothelial cells, but was less noticeable in epithelial cells, where a small number of surviving cells were able to divide and re-form confluent monolayers. An anomalous finding was cell death in keratocyte cultures 3A, 3B, 4A, and 4B. Their parent cultures 3 and 4, inoculated at the lowest MOI (0·01 PFU/cell) were subcultured on day 13. On day 14 the progeny cultures were transferred to 37°C and medium was replaced by medium supplemented with 5% human serum. The cells had not settled on to the culture flasks by day 14 and were removed with the medium. Other keratocyte cultures 5A-8B, subcultured on day 13 but left undisturbed at 41·5°C until day 16, settled and ultimately became confluent. (Table 1, a-c, column 2).

Persistent infection, defined as the presence of infectious virus in the supernatant medium at 41·5°C, after the immediate period after infection, was detected in one epithelial cell culture infected at 0·01 PFU/cell and four epithelial cell cultures infected at 0·1 PFU/cell. The infection appeared to be partially suppressed in that it did not succeed in destroying cellular monolayers until cells were transferred to 37°C. No infectious virus was detected in surviving

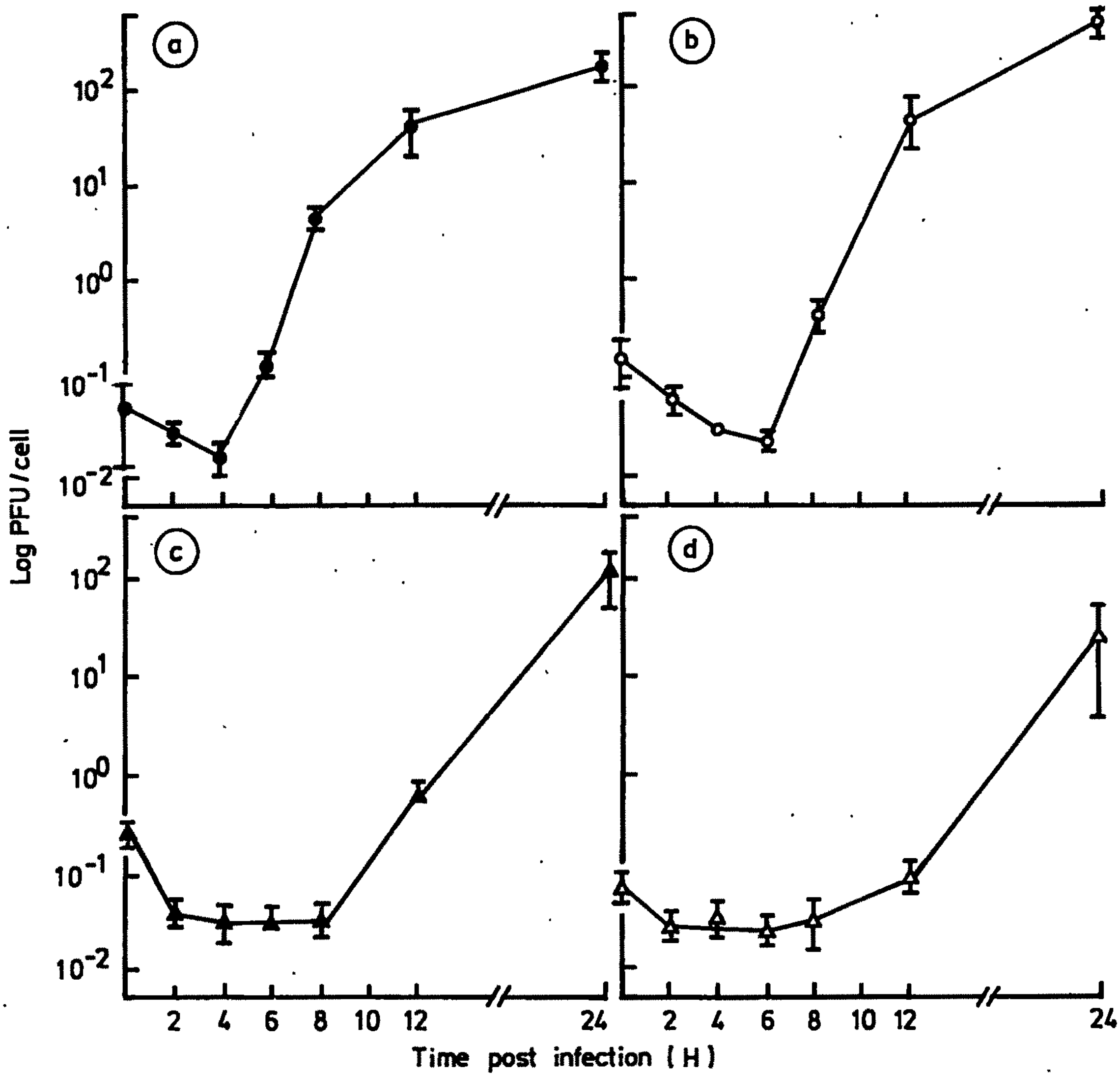

Fig. 1 *One-step growth curves of HSV-1, Glasgow 17 strain in* (a) *BHK21 C13 cells,* (b) *epithelial cells,* (c) *keratocyte cells, and* (d) *endothelial cells. Cells were infected at an MOI of 10 PFU/cell. After absorption for 1 hour at 37°C the monolayers were washed twice with PBS C5, overlaid with EC10, and incubated at 37°C (see 'Material and methods'). Cultures were harvested at the times indicated and the virus titre measured by plaque assay on BHK21 C13 cells.*

keratocyte and endothelial cell cultures maintained at 41·5°C for up to 28 days after infection (Table 1a-c, column 4).

Latent infection was defined as absence of infectious virus in the supernatant medium at 41·5°C, but detectable infectious virus in the supernatant medium after transfer to 37°C. All cell types proved capable of releasing infectious HSV after human serum was removed at 37°C (Table 1, a-c, column 5).

By day 40 after infection all surviving epithelial cells had released infectious virus, but five keratocyte and three endothelial cell cultures at 37°C had failed to release virus up to 20 days after removal of human serum. The eight cultures that failed to release infectious virus at 37°C were defined as reactivation failures (Table 1a-c, column 6). The release of infectious virus was quicker from epithelial cells and endothelial cells than from keratocytes after human serum was removed (Table 1a-c, column 7).

Table 1a *Course of non-productive infections in corneal cells: epithelium*

Culture number	*Culture death*	*No. of days at 41·5°C*	*Persistent infection*	*Latent infection*	*Reactivation failure*	*Time of virus release after HS removal at 37°C (days)*
1*		7		+		3
2		7		+		3
3		14		+		2
4		14		+		2
5		21		+		6
6		21		+		9
7		28	+			
8		28		+		2>
9A†§		7		+		3
9B		7		+		3
10		7		+		3
11		14	+			
12		14	+			
13		21		+		3
14		21	+			
15		28	+			
16		28		+		2
17‡	C<	7				
18		7		+		3
19		14		+		4
20		14		+		4>
21		21		+		9
22		21		+		3
23		28		+		2
24		28		+		2

See footnote to Table 1c.

CELLULAR STRESS PROTEINS

As stated above, supraoptimal temperatures induce the synthesis of cellular stress proteins. Other agents including disulfiram,[39] transition series metals, and sulphydryl reagents induce the synthesis of cellular stress proteins.[38] Fig. 2 shows the effect of temperature elevation on protein synthesis in rabbit corneal epithelial cells and keratocytes. Disulfiram 0·3 μM has been added to the cell growth medium at 37°C to obtain radiolabelled stress protein markers. In mock infected keratocytes and epithelial cells, incubated at 41·5°C, there was increased synthesis of proteins with approximate molecular weights of 90 000, 75 000, and 43 000. Novel proteins with approximate molecular weights 70 000, 63 000, 53 000 and 45 000, also appeared to have been synthesised.

Many characteristic herpes simplex virus proteins were detected after 24 hours in both keratocyte and epithelial cells infected at 20 PFU/cell and maintained at 37°C; however, these were absent at 41·5°C. The herpes simplex virus infected cells at 41·5°C had similar protein profiles to those of the mock infected cells at 41·5°C.

Table 1b *Course of non-productive infections in corneal cells: keratocytes*

Culture number	*Culture death*	*No. of days at 41·5°C*	*Persistent infection*	*Latent infection*	*Reactivation failure*	*Time of virus release after HS removal at 37°C (days)*
1A*§		7		+		3
1B		7		+		3
2A		7		+		3
2B		7		+		3
3A	+	14				
3B	+	14				
4A	+	14				
4B	+	14				
5A		21			+	
5B		21		+		6
6A		21			+	
6B		21		+		6
7A		28			+	
7B		28			+	
8A		28			+	
8B		28		+		5
9†		7		+		6
10		7		+		11
11		14		+		13
12		14		+		2>
13	+	21				
14	+	21				
15	+	28				
16	+	28				
17‡		7		+		9
18		7		+		23
19		14		+		7
20	+	14				
21	+	21				
22		21		+		1>
23		28		+		>
24	+	28				

See footnote to Table 1c.

Discussion

In man the cornea is a site where recurrent herpetic disease occurs. We have grown separate cultures of rabbit corneal epithelial cells, keratocytes, and endothelial cells whose purity has been defined both morphologically and by cell specific markers. The three cell types have been used initially to study the lytic cycle of HSV-1 in corneal cells and secondly to establish an in-vitro latency system in cells where the virus is known to occur in vivo.

Previous in-vitro latency models have used HEL-F cells and cytosine arabinoside,[20] rat fetal neurones and BVdUR plus interferon,[21] and human fetal neurones and BVdUR plus interferon,[24] to examine virus and cell specific functions related to latency. All these systems employed viral inhibitors. Temperature elevation alone has been shown to induce latent

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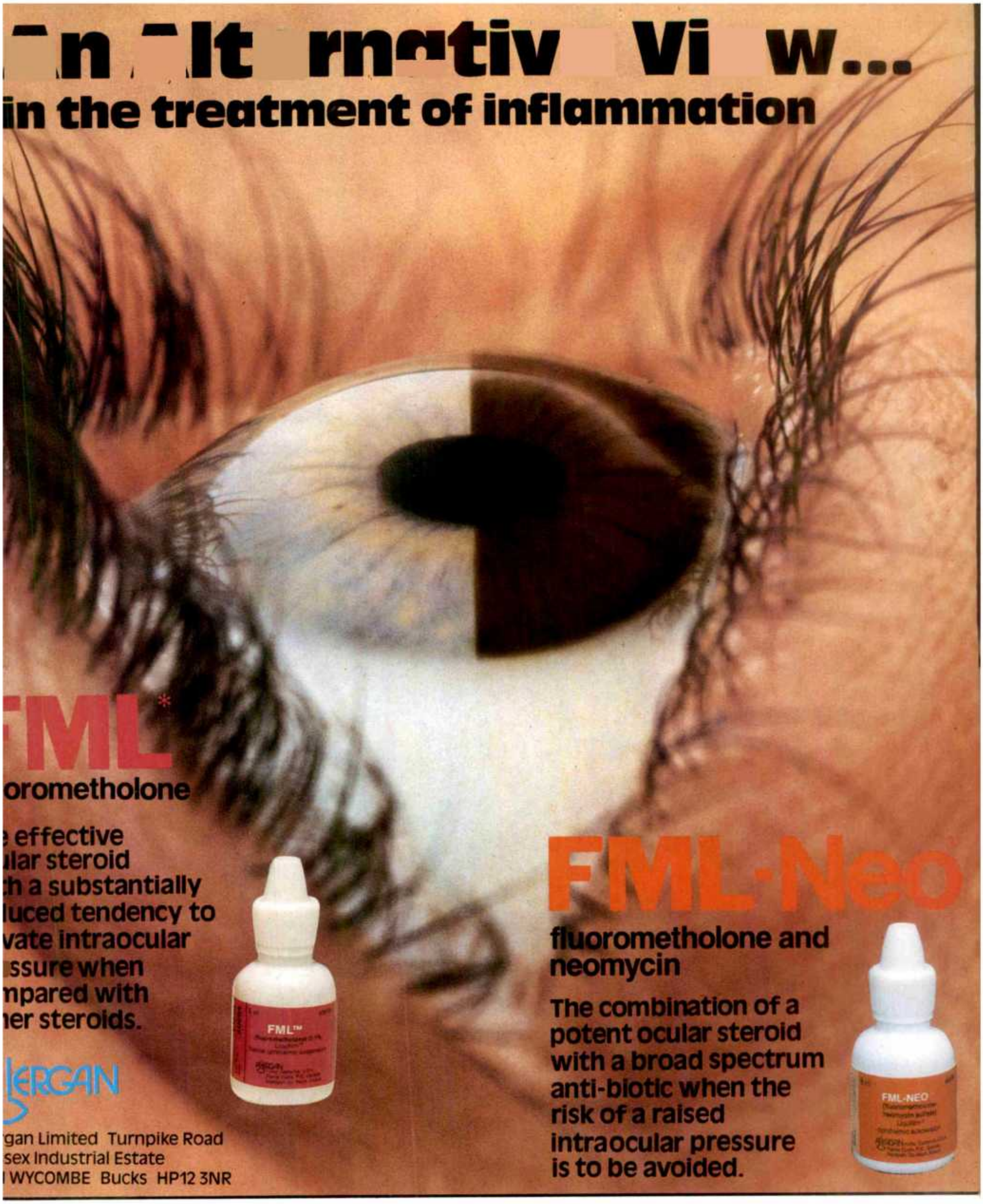

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e dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.
ications, Warnings, etc. CONTRA-INDICATIONS: Acute superficial herpes simplex keratitis. Fungal diseases of ocular
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tituents of this medication. **Warnings** Steroid medication in the treatment of herpes simplex keratitis (involving the
uires great caution; frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the
, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of
ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or
oration has been known to occur with use of topical steroids. Safety and effectiveness have not been demonstrated in
the age group two years or below. This preparation contains benzalkonium chloride and should be used with caution in
with hydrophilic contact lenses. **Use in Pregnancy** Safety of the use of topical steroids during pregnancy has not been
. **Precautions** As fungal infections of the cornea are particularly prone to develop coincidentally with long-term steroid
s, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intra
sure should be checked frequently. **Adverse Reactions** Glaucoma with optic nerve damage, visual acuity or field defects,
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Presentation Sterile, white, microfine ophthalmic suspension containing fluorometholone NF0.1% and neomycin sulphate BP0.5% (equivalent to 0.35% neomycin base). **Uses** FML-NEO* is indicated for the management of steroid responsive inflammation of the palpebral or bulbar conjunctiva, cornea and anterior segment of the globe, when threatened or complicated by infection with neomycin-sensitive organisms. **Dosage and Administration** One or two drops in the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosage may be safely increased to one drop every hour. Care should be taken not to discontinue treatment prematurely. Shake well before using. **Contra-indications, Warnings etc.** Acute untreated purulent ocular infections. Acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the conjunctiva and cornea. Ocular tuberculosis, fungal diseases of the eye and hypersensitivity to any of the components of the drug. **Warnings** As for FML* above and, in addition in diseases due to micro-organisms resistant to neomycin, infection may be masked enhanced or activated by the steroid. Prolonged use may result in overgrowth of nonsusceptible organisms. Articles in current medical literature indicate an increase in the prevalence of persons sensitive to neomycin. The possibility of such a reaction should be borne in mind. If sensitivity or other untoward reactions occur, discontinue the medication. **Precautions** Patients with histories of herpes simplex keratitis should be treated with caution. Use of topical steroids may increase intraocular pressure. Safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated. Local side effects of steroid therapy ie skin atrophy, striae and telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Shake well before using. Do not freeze. **Legal Category** POM. **Package Quantities** Available in 5ml plastic dropper bottles. Basic NHS cost (as at July 1984) £1.90. PL 0426/0043. Full Prescribing information is available on request.

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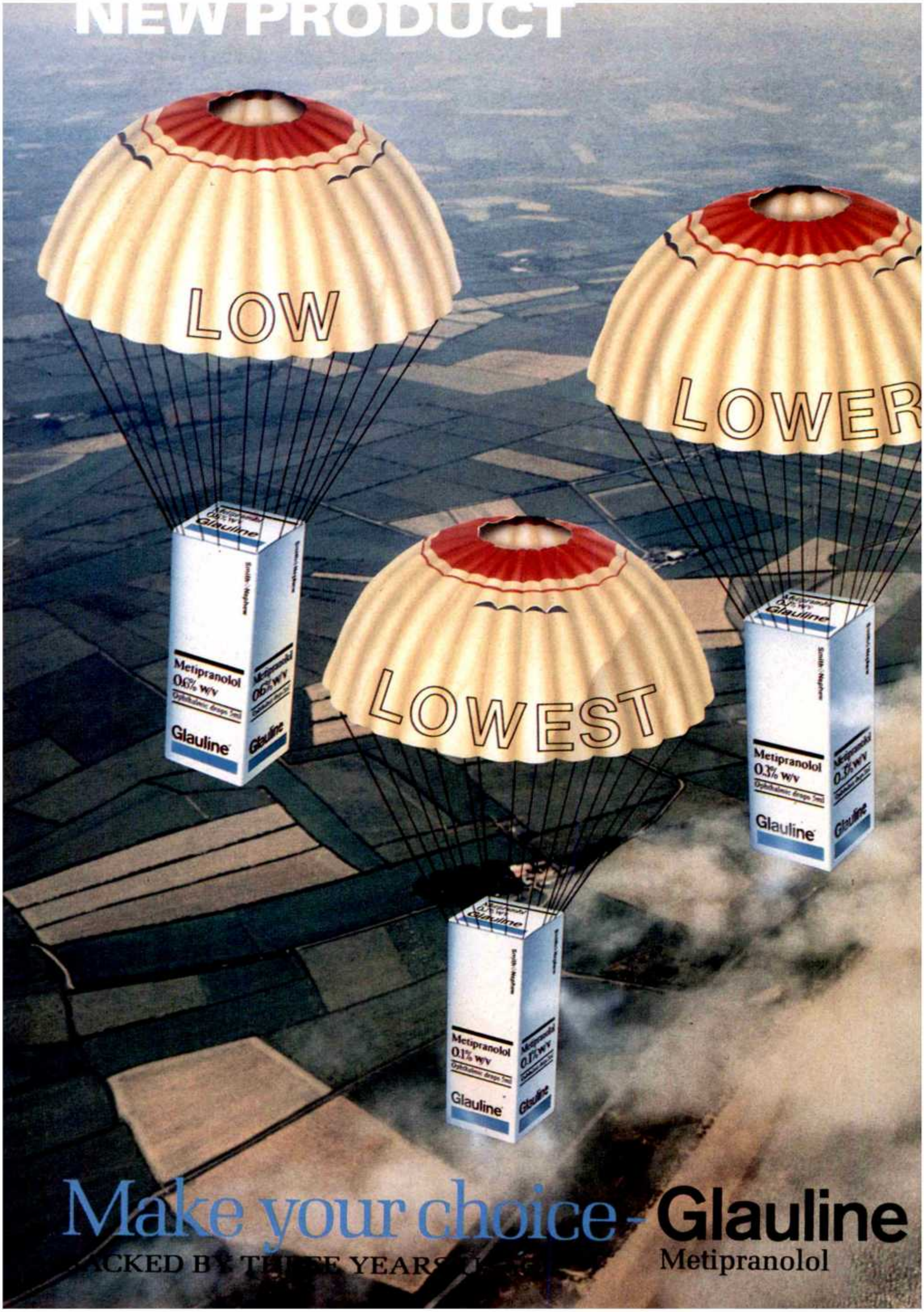
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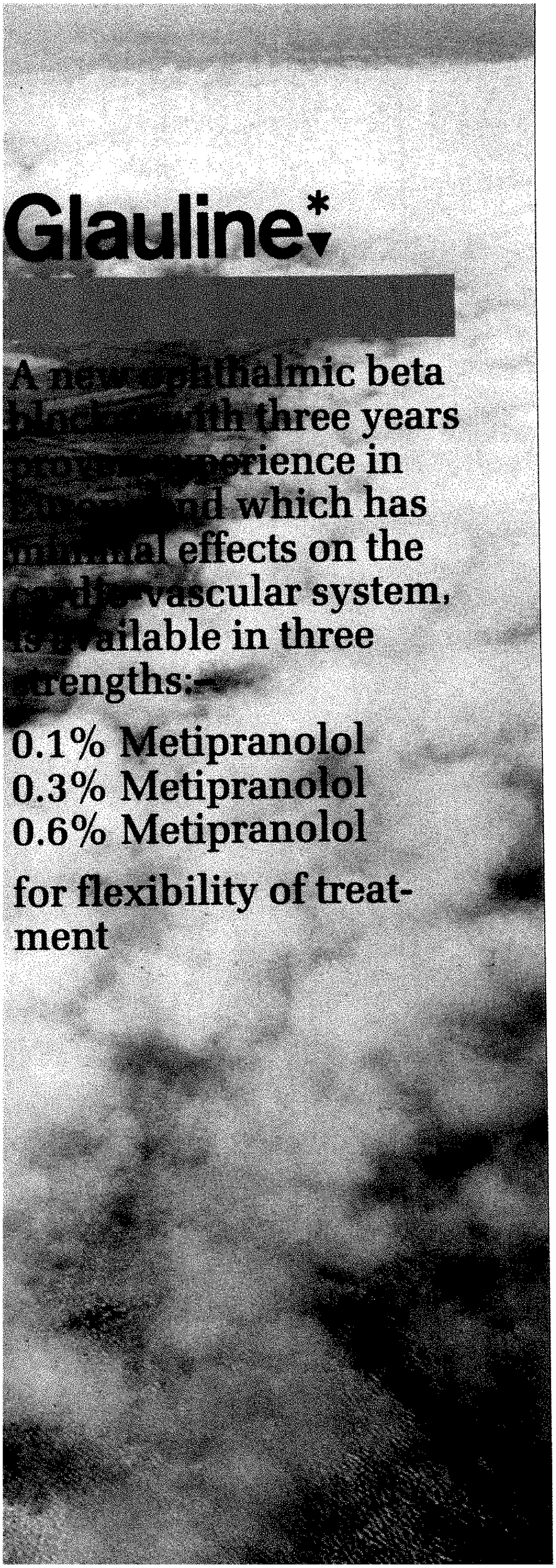

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PHARMACEUTICAL PRECAUTIONS

Glauline should not be diluted or dispensed from any container other than the original bottle. It is potent for three years unopened, but as with other eye drops the contents of each bottle should be discarded one month after opening.

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FURTHER INFORMATION

Glauline has little or no effect on pupil size or accommodation.

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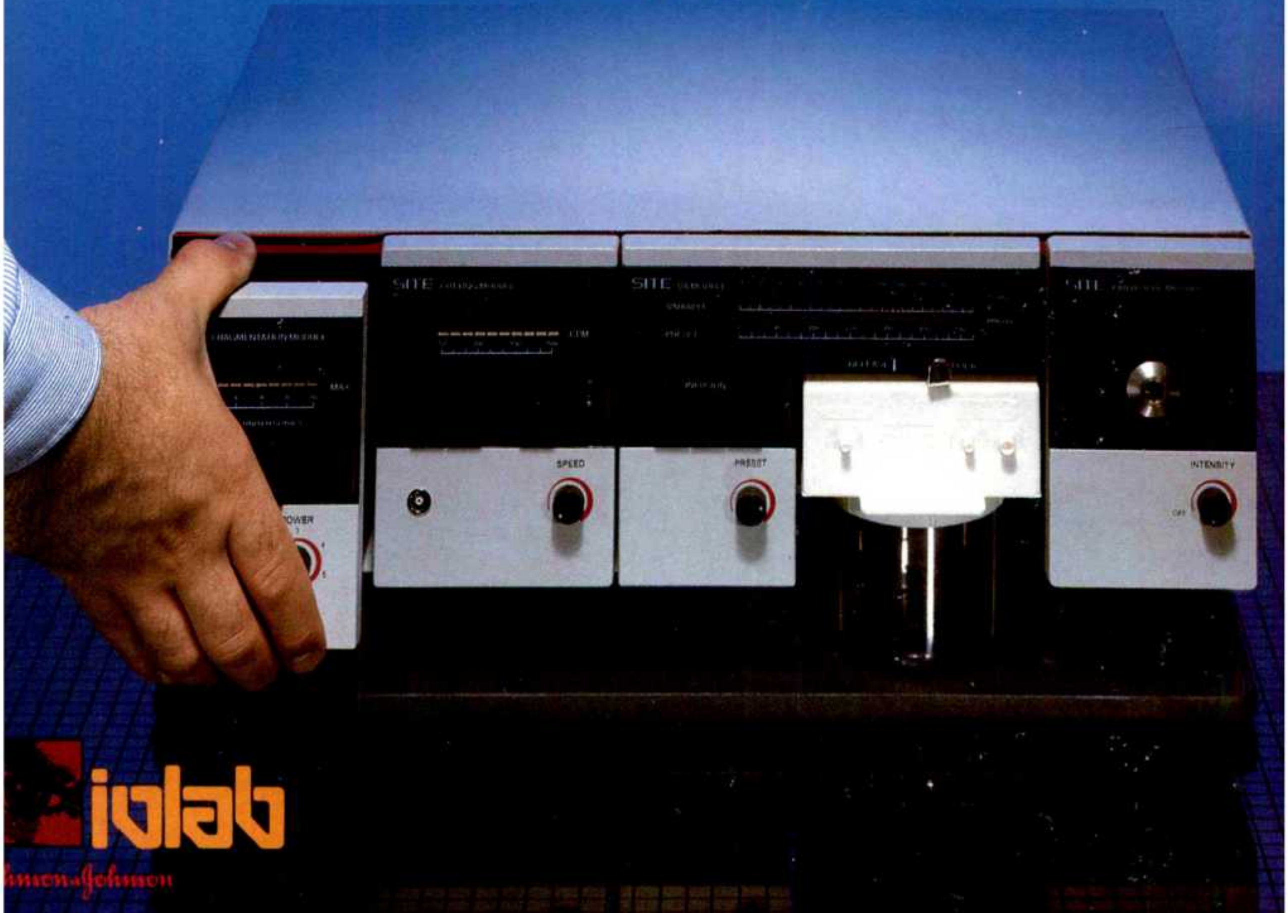

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Table 1c *Course of non-productive infections in corneal cells: endothelium*

Culture number	*Culture death*	*No. of days at 41·5°C*	*Persistent infection*	*Latent infection*	*Reactivation failure*	*Time of virus release after HS removal at 37°C (days)*
1*		7		+		9
2A§		7		+		3
2B		7		+		3
3		14			+	
4		14		+		2
5		21		+		6
6		21		+		9
7		28		+		2
8		28			+	
9A†		7		+		3
9B		7		+		3
10		7		+		3
11	C<	14				
12		14		+		2
13A		21			+	
13B	C	21				
14		21		+		3
15		28		+		2
16A	+	28				
16B	+	28				
17‡	C	7				
18		7		+		9
19		14		+		7
20	+	14				
21	+	21				
22		21		+		3
23		28		+		5
24		28		+		2

*Cultures 1–8, MOI 0·01 PFU/cell. †Cultures 9–16, MOI 0·1 PFU/cell. ‡Cultures 17–24, MOI 1·0 PFU/cell. §A or B: Cultures were split 1:2 on day 13. <C: Cell death occurred owing to contamination. >Cultures shed virus at 37°C in the presence of human serum; keratocyte culture 23 did not shed any other virus at 37°C.

viral infection in HEL-F cells.[26] The in-vitro latency system reported here is solely dependent on manipulation of temperature to induce and reactivate latent HSV-1 infections. The in-vitro latency system was used to determine whether peripheral cells, which are a known focus of recurrent disease in man, are capable of supporting latent HSV infection.

The viral growth rate was fastest in epithelial cells and closely resembled that in control BHK 21 C13 cells. The growth rate was intermediate in keratocyte cells and slowest in endothelial cells. Experiments by Carter *et al.*[40] using corneal cells infected with HSV at lower MOIs suggested that virus titres reached their maximum in 24 hours and then remained relatively constant until 72 hours. It can be concluded that corneal epithelial, keratocyte, and endothelial cells were capable of efficiently supporting HSV replication.

Our experiments have shown that the three corneal cell types were capable of replication under heat shock conditions (Table 2, column 1). Splitting cultures 1:2 at 41·5°C did not induce detectable reactivation of infectious virus. In our in-vitro latency system the multiplicity of infection was found to be critical; when 0·1, 1·0 PFU/cell was used, a very large proportion of cells were killed in the immediate seven days after infection. This effect was overwhelming in some keratocyte and endothelial cell cultures, leaving no surviving cells (Table 2, column 2). The findings were comparable with the results of O'Neill *et al.*,[20] who found that the innoculating MOI was critical to ensure surviving cells. Wigdahl *et al.*[24] have successfully increased the MOI by using a combination of the antiviral drug BVdUR and interferon to treat cells pior to infection with HSV.

Epithelial cells were the only cell type to exhibit persistence, defined as a detectable chronic low-grade viral infection, insufficient to destroy the cellular monolayer at 41·5°C (Table 2, column 3). The three corneal cell types could support latent HSV infection, defined by absence of infectious virus in supernatant medium at 41·5°C assayed on BHK21 C13 cells but presence of infectious virus in supernatant medium at 37°C assayed on BHK21 C13 cells (Table 2, column 4). Virus was released more quickly from epithelial cells and endothielial cells than from keratocytes at 37°C (Table 2, column 6).

Corneal cell types have different properties of replication in vivo, with epithelial cells dividing and being shed throughout life whereas keratocytes have replicative potential but tend to be stable, and endothelial cells have limited if any replicative ability in vivo.[30 31] It is established that HSV latency occurs in non-dividing neurones in vivo, both in man[1 2] and in animals.[3 4] Wigdahl *et al.*[41] showed in an in-vitro system that neurones were capable of supporting more latent HSV genomes per haploid cell than HEL-F cells. We have shown in our in-vitro system that keratocyte and endothelial cells which are non-dividing in vivo are capable of maintaining a latent HSV infection. Epithelial cells are also capable of maintaining an in-vitro latent HSV-1 infection, but in addition epithelial cells showed some persistent HSV infection at 41·5°C. No surviving epithelial cell cultures failed to release infectious HSV on transfer to 37°C, in contrast to keratocyte and endothelial cultures, where eight cultures in total did not release infectious virus at 37°C (Table 2, column 5). It is possible that non-inducible herpes simplex virus was present in these cultures and might have been detected by viral superinfection experiments.

The mechanisms regulating viral latency are still unclear. In our in-vitro latency system only temperature elevation or reduction has been used to induce

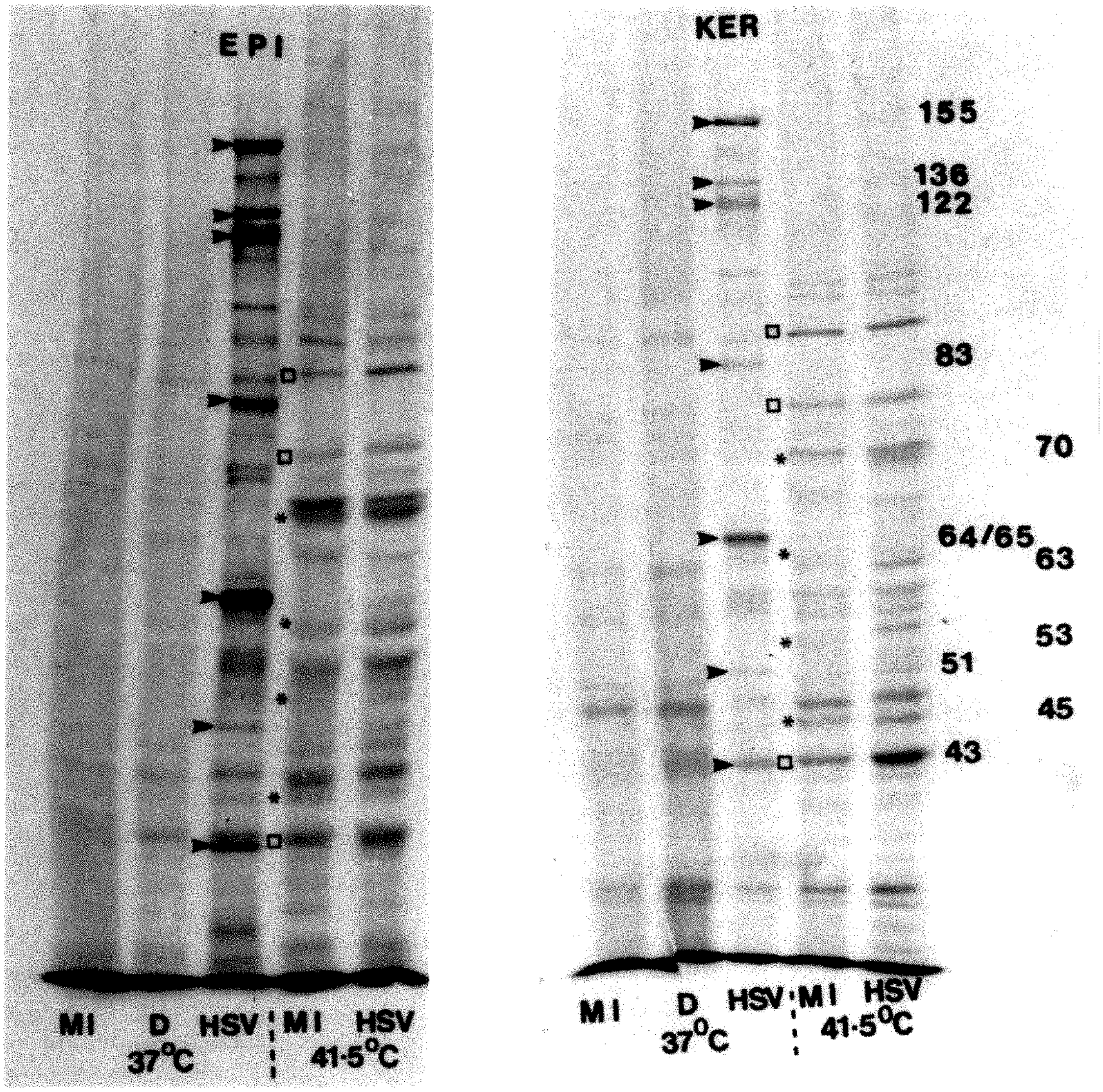

Fig. 2 *Protein synthesis in rabbit corneal epithelial cells and keratocytes. Cultures were mock infected* (MI), *treated with 0.3 μM disulfiram* (D), *or infected with herpes simplex virus at 20 PFU/cell (HSV). Cultures were maintained at 37°C or 41·5°C.* ☐ *Increased synthesis of cellular stress proteins.* * *Synthesis of novel stress proteins.* ▶ *Synthesis of HSV induced proteins. Approximate molecular weights of HSV proteins are given on the near right of the last track. Approximate molecular weights of stress proteins are given on the far right.*

Table 2 *Cumulative data of non-productive infections in corneal cells*

	Total no. of cell cultures	*% Culture death (including contamination)*	*% persistent infection*	*% Latent infection*	*% Reactivation failure*	*Means of virus release at 37°C after HS removal (days)*
Epithelium	25	4	20	76	0	3·6
Keratocytes	32	34	0	50	16	6·3
Endothelium	28	25	0	64	11	4·2

latency or trigger reactivation. Heat shock induces stress proteins.[27] Notarianni and Preston[28] have shown that stress proteins are induced by the immediate early proteins of HSV. In our system most cellular stress proteins were induced by heat shock. It was not possible to ascertain whether additional proteins were induced in any of the three cell types infected at low MOI with HSV. However it is clear that cellular stress proteins were present at 41·5°C when HSV is latent and were much reduced in intensity at 37°C when virus was able to reactivate. This virus/cell interaction may well have a role in the control of viral latency.

The study of latency in separated corneal cells promises to be of value in the understanding of problems posed in herpes simplex virus keratitis. Our results support the hypothesis that non-neural cells are capable of maintaining latent HSV infection.

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Clinical and electrophysiological observations in patients with low pressure retinopathy

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SUMMARY The clinical, angiographic, and electrophysiological features of seven patients with transient visual loss and low-pressure retinopathy are presented. Six of the patients also had symptoms of cerebral ischaemia. The commonest provoking feature was bright light. Angiography showed multiple extracranial occlusions involving both internal and external carotid arteries in addition to occlusion or stenosis on the contralateral side. Electroretinography showed delay in the recovery of the b wave in the affected eye after exposure to bright light. This appears to be a valuable test for the detection of minor degrees of ischaemic damage to the retina caused by insufficiency of the retinal and choroidal circulation.

Kearns and Hollenhorst[1] first pointed out that an unusual type of haemorrhagic retinopathy (venous stasis retinopathy) may occur in patients with carotid artery occlusion from perfusion of the retina at an abnormally low arterial pressure. If unrelieved the condition may progress to loss of sight from the ischaemic and haemorrhagic consequences of vascular closure and neovascularisation; the anterior segment of the eye may also become involved.[2]

Increasing use of digital subtraction angiography has identified many patients with unsuspected multiple extracranial artery disease at the time when they have suffered only minor symptoms. This report reviews the clinical features of seven patients with episodic visual loss caused by temporary retinal

Table 1 *Clinical and angiographic features of low pressure retinopathy*

Patient	*Sex*	*Age*	*Arterial lesion*	*Transient visual symptoms*	*Provocation*	*Other features*
1	M	70	Atheroma: LIC occlusion RIC stenosis	Daily, uniocular L eye; fragmentation, excessive contrast	Light, heat, standing, exertion	No cerebral symptoms, cerebral border zone infarct (CT)
2	F	59	Atheroma: LCC occlusion	1–2/day uniocular L eye; blurring	Light, standing, walking	'Tonic' L pupil, L hemisphere TIA and completed stroke
3	M	72	Atheroma: bilateral ICA occlusion	Both eyes; dazzle	Light	TIA unilateral L 'tonic' pupils
4	M	62	Atheroma: LCC occlusion RIC stenosis	Two per week uniocular L eye; flashing lights frosted glass	Light, looking upwards	TIA L hemisphere
5	F	53	Atheroma: RIC occlusion	Daily, uniocular R eye; central coloured flashing, fragmentation	Light	TIAs and completed stroke (CT), border zone infarct
6	M	59	Atheroma: RIC occlusion REC stenosis	Recurrent uniocular R eye; blurring	Nil	Localised infarct R hemisphere
7	M	54	Atheroma: LCC occlusion RIC stenosis	Daily dazzling L eye; contrasting kaleidoscope contraction of field	Heat, sunshine, looking upwards, neck extension, hot meal	TIA L hemisphere

LIC, RIC = left, right internal carotid artery. LCC, RCC = left, right common carotid artery. ICA = internal carotid artery. REC = right external carotid artery. TIA = transient ischaemic attack. CT = computer tomography.

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insufficiency. The diagnostic value of the electroretinogram (ERG) is emphasised: it may point to the underlying mechanism causing transient loss of sight.

Patients and methods

The seven patients described here were selected from a total of 23 patients having venous stasis retinopathy. The remainder either had no visual symptoms or a fixed visual deficit.

Results

VISUAL SYMPTOMS (Table 1)

Our patients had transient visual disturbances, uniocular in six and binocular (at different times) in one. In five patients the attacks consisted of a distortion, fragmentation, or dazzling sensation. They described visual images as excessively 'contrasty' as in an incorrectly developed negative film. In addition brief central flashes of light were experienced by two patients. The remaining two patients simply described the attacks as temporary blurring of vision without special features.

The visual symptoms developed over half to one minute and continued for five to 15 minutes.

All the patients were questioned about the circumstances of onset of their attacks and for environmental events which could provoke symptoms (Table 1). Six of the seven patients noticed provocation of attacks by bright light, especially on going out into strong sunlight. Two patients mentioned postural factors such as suddenly standing upright or the onset of exertion. Two found attacks to occur on upward movement of the eyes and one on extension of the neck. Only one patient felt that the attacks occurred at random.

RETINAL APPEARANCES

All patients showed the ophthalmoscopic appearances of venous stasis retinopathy as previously described. These comprised peripheral blot haemorrhages, microaneurysms, and venous dilatation and 'beading' (Figs. 1A,B). Laminar streaming giving the appearance of red borders to the major veins was noted in some patients. In all cases the pressure in the central retinal artery was reduced, so that the artery collapsed with minimal digital pressure on the globe.

Fluorescein angiography demonstrated many peripheral microaneurysms which could not be seen with the direct ophthalmoscope. There was marked prolongation of arteriovenous transit times and venous leakage from veins near the posterior pole in two cases (Figs. 1C–E). Patchy regions of non-filling were evident in the choroidal circulation.

ANGIOGRAPHY

The results of angiography, either by arch angiography with retrograde arterial catheterisation (four patients) or by the intravenous digital subtraction technique (three patients) are shown in Table 1. The intravenous method gave satisfactory visualisation of the extracranial arteries in each case.

ELECTROPHYSIOLOGICAL TESTS

The standard ERG parameters[3] in four patients with unilateral symptoms showed constant minor abnormalities on the affected side (Table 2). In one patient who had attacks in both eyes no difference was apparent.

The b wave of the ERG evoked by flashes of equal intensity increases in amplitude with time in the dark, reaching a plateau level, but falls practically to zero when the eye is exposed to a bright photoflood lamp

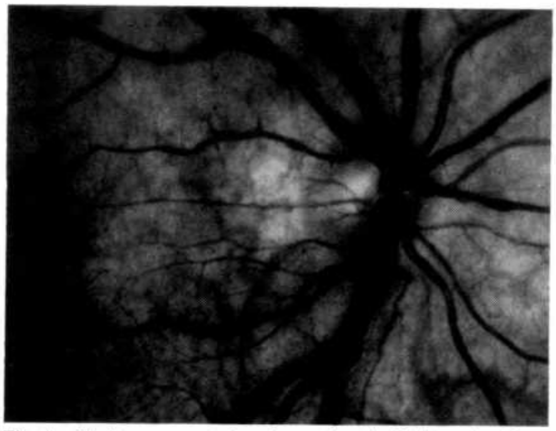

Fig. 1 *Right venous stasis retinopathy. A: Right retina disc region to show venous dilatation.*

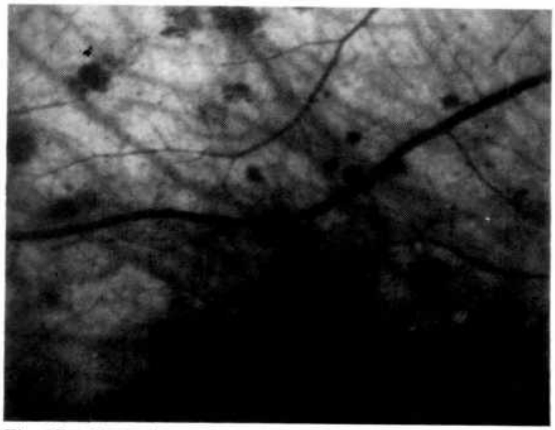

Fig. 1B *Retinal periphery showing multiple round haemorrhages.*

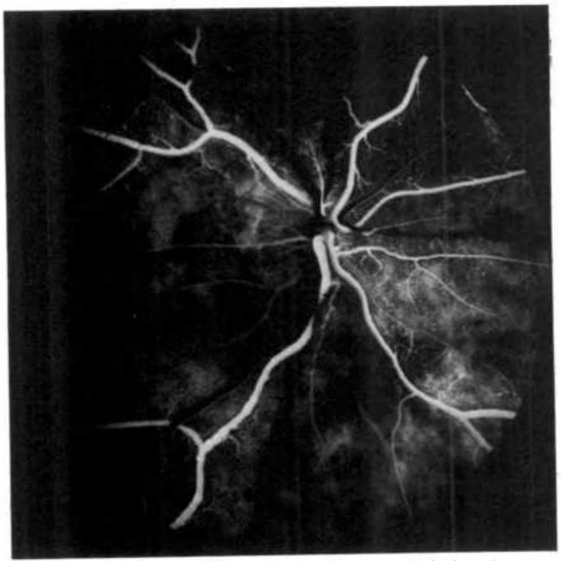

Fig. 1C *Fluorescein angiography (late arterial phase) showing delayed venous filling, arterial beading (lower temporal branch), microaneurysms, and patchy choroidal filling.*

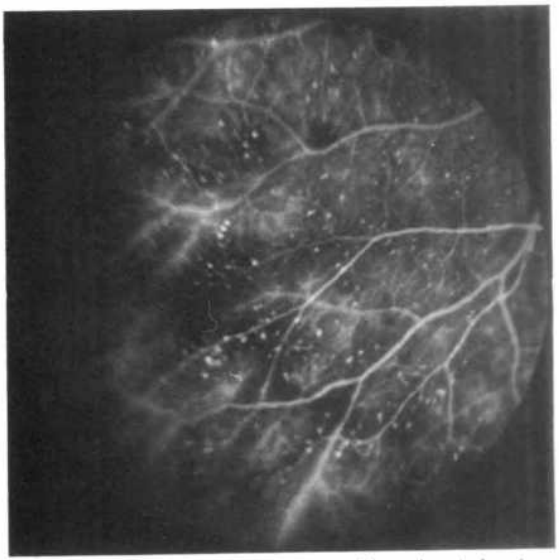

Fig. 1D *Fluorescein angiogram (capillary phase) showing many capillary microaneurysms adjacent to arterioles and leakage of dye from venules.*

for 30 seconds. Recovery of the previous b wave amplitude takes place gradually over the subsequent 10–12 minutes in a normal eye.

In all four patients with unilateral symptoms there was a marked prolongation of the time taken after photostress to regain the previous b wave amplitude in the affected eye when compared with the other side (Table 3). A single patient with attacks in either eye showed a smaller difference.

In addition the light induced change in the corneo-fundal potential was determined by electro-oculographic (EOG) methods in four out of the five patients on whom the ERG photostress tests were carried out (Table 4). The light peak of the EOG is generated by the slow increase in transpigment epithelial potential after photoreceptor response to light and is a measure of functional integrity of choroid, pigment epithelium, and photoreceptors. The EOG light rise was lower and the peak time longer in the affected eyes than in the comparison (less affected) eyes in all patients, though the number of cases was small and the difference was not statistically significant.

OTHER CLINICAL FEATURES

Two patients (Table 1) had abnormal pupils. These were large, circular, and reacted slowly both to light and to convergence. Both of these patients had attacks of visual loss on exposure to bright light. Six of the seven patients had cerebral symptoms. In three these consisted only of transient cerebral ischaemic attacks, in two there were ischaemic attacks in addition to a minor stroke. In all cases the affected hemisphere was on the same side as the carotid occlusion. The patients who sustained permanent deficits showed areas of localised cerebral infarction on CT scan. These were situated in the parieto-occipital border zone between middle and posterior cerebral artery territories.

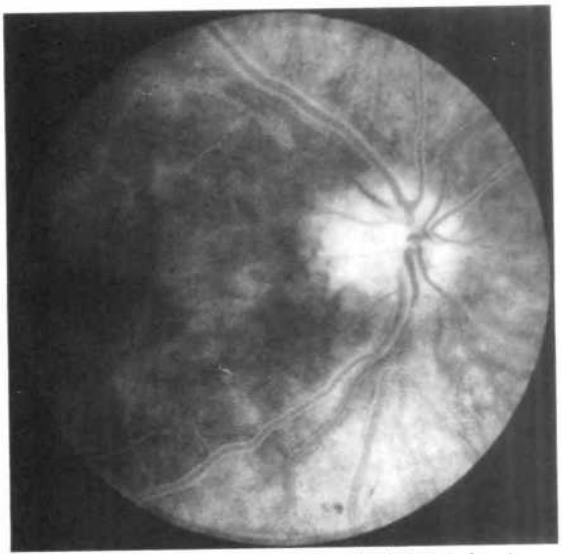

Fig. 1E *Fluorescein angiogram (residual phase) showing abnormal leakage from optic disc and round large veins.*

Table 2 *ERG parameters in four patients (bilateral recording). Patient 3 had attacks on either side*

Patient	*Sex*	*Age*	*Affected eye*	*Slope of ERGs dark adaptation*	*Scotopic b wave threshold**	*Maximum b wave (μV)*	*b/a wave ratio*	*Flicker ERG wavelets amplitude (μV) at 30 Hz*	
								Deep red	*Bright white*
Lower limit of normal range				1·2	4·7	520	2·3	75	175
5	F	72	RE	R 1·0	1·7	400	1·6	25	50
				L 1·2	4·2	450	1·8	50	100
1	M	70	LE	R 0·9	4·0	320	2·0	20	50
				L 0·7	3·5	220	1·8	2	20
4	M	62	LE	R 1·0	4·7	400	2·0	70	120
				L 0·8	4·0	300	1·8	50	70
3	M	72		R 1·0	4·7	500	1·2	60	125
bilat. L>R				L 0·9	4·7	550	1·2	60	125

*The value of neutral density filter in log units when used to reduce the intensity of R stimulus flash to evoke just measurable scotopic b wave of the ERG.

Table 3 *b Wave recovery time in five patients with low pressure retinopathy (bilateral recording). Patient 3 had bilateral attacks. Left was worse than right. The right was considered as comparison*

Patient	*Comparison eyes*	*Affected eyes*
5	12 min	18 min
1	16 min	22 min
4	11 min	20 min
2	18 min	24 min
3	18 min	21 min
Mean	15·0 min	21·0 min
SEM	1·5 min	1·0 min

$p<0·01$ (Student's paired *t* test).

Table 4 *EOG light rise and light peak time in four of five patients with low pressure retinopathy listed in Table 3. (The lowest limit of normal EOG light rise is 250% and peak time between 7 and 9 minutes)*

Patient	*Comparison eyes, light rise in %* (peak time)*	*Affected eyes*
1	170% (10 min)	136% (11 min)
4	250% (9 min)	220% (10 min)
2	170% (9 min)	133% (10 min)
3	205% (10 min)	190% (12 min)
Mean	199% 9·5 min	170% 10·8 min
SEM	19% 0·3 min	21% 0·5 min

EOG light rise $p>0·05$ (NS). Peak time $p<0·05$.
*The light rise is calculated by the formula:

$$\frac{\text{Peak potential in light}}{\text{Main potential in dark}} \times 100.$$

Discussion

Brief attacks of retinal or cerebral ischaemia are a well known feature of atheromatous disease of the internal carotid artery, and both clinical and pathological evidence points to embolism of mural thrombus as the likely mechanism in the majority of patients.[4] The present report concerns a group of patients who also experience ischaemic attacks in the brain and eye but in whom the underlying mechanism is different and is caused by a local breakdown in vascular homoeostasis (retinocerebral insufficiency).

The main differences between embolic and insufficiency attacks are in the duration, the clinical expression, and the circumstances in which they occur. An embolic attack consists of the random occurrence of a black or dense cloud rapidly spreading in a vertical direction over the whole or half of the field of vision, persisting for a few minutes, and occurring without systemic or cerebral symptoms. Insufficiency attacks on the other hand are generally of a longer duration, less rapid onset, and may be accompanied by symptoms of generalised or localised cerebral oligaemia in the form of faintness, focal weakness, or jerking of the limbs.[5] The visual disturbance is described in terms of distortion or fragmentation of the field of vision, often with dazzling. The 'shutter' effect which is characteristic of embolic occlusion seldom occurs, though some patients may describe centripetal contraction of the field. Provocation by circumstances which either reduce retinal arterial pressure or raise retinal venous or intraocular pressure is a feature of insufficiency in some patients. These circumstances include rapidly standing upright, beginning to walk, stooping, movements of the neck, or sustained upward gaze. Provocation by bright light is a special feature of retinal insufficiency and is discussed below.

OCULAR FINDINGS

The present report confirms the descriptions already given of venous stasis retinopathy.[1] In addition to the main features of venous dilatation, peripheral haemorrhages, and microaneurysms we noted arterial irregularity (Fig. 1C) and laminar streaming of red venous blood in some of the larger retinal veins, possibly an indication of uneven rates of flow through different retinal regions or a disturbance of the normal coupling between flow and metabolism. A similar appearance has been described in the pial circulation in states of acute ischaemia.[6] Fluorescein angiography demonstrates perivenous leakage at the posterior pole, and many clusters of peripheral microaneurysms which could not be discerned through the ophthalmoscope (Fig. 1C). A simple bedside estimation of ophthalmic artery pressure by digital pressure on the globe showed a gross reduction in all cases, and this constitutes the single most important diagnostic physical sign. We found the pressure too low for reliable ophthalmodynamometry.

ANGIOGRAPHY

The existence of four large low-resistance arteries supplying the brain allows occlusion of a single vessel to occur without a major reduction in total cerebral blood flow. When the internal carotid artery is occluded, there are two major alternative pathways: firstly, the contralateral internal carotid via the circle of Willis, and secondly the ipsilateral external carotid via the orbital anastamoses. In all but one of the present series in addition to complete occlusion of the internal carotid artery there was occlusion of other vessels, compromising one or both of these collateral pathways. Only one patient was found to have an isolated occlusion of the internal carotid artery, and it must be presumed in this case that there was incomplete development of the anterior part of the circle of Willis, with aplasia or hypoplasia of the anterior cerebral artery on one side.

PATHOGENESIS

Electrophysiological testing on patients whose attacks affected one eye and in whom the other eye acted as a control gave some insight into the mechanism of retinal insufficiency. Minor differences in the ERG in the form of scotopic b wave threshold, slope of ERG, or reduced b wave amplitude were seen and were consistently more marked on the affected side. The finding that EOG light rise was significantly lower (mean 170%) and slower (10·8 minutes) than normal (250%, 7–9 minutes) suggests that the physiological lesion is already present at the interface between choroid, pigment epithelium, and photoreceptor outer segment in these patients with low pressure retinopathy. However, the most helpful diagnostic test was the comparison of the time taken in each eye for recovery of the amplitude of the b wave following exposure of the eye to photostress. Prolongation of the recovery time by over three minutes was found in all patients having unilateral attacks.

Two possible interpretations of these findings are suggested. The first is that resynthesis of visual pigment after bleaching causes an increase in retinal metabolic rate, and when the supply of oxygen or substrate cannot keep pace with metabolic demand the time needed to recover from photostress is prolonged.[7] There is a close analogy here with angina pectoris or intermittent claudication. However, there is little evidence that retinal metabolic requirements do change significantly in different light conditions,[8] and an alternative explanation may simply be that the delayed recovery after photostress is a non-specific finding, indicating mild but permanent damage to the outer retinal layers and pigment epithelium. Indeed the light evoked electrical responses of the retinal pigment epithelium and photoreceptors are extremely sensitive to hypoxia and show slower and less complete recovery.[9] The question may be resolved by applying the test to other types of retinal disease not caused by arterial insufficiency or by repeating the test after vascular insufficiency has been corrected.

The time taken to recover normal visual acuity after exposure to photostress is a clinical measurement which has been used in the diagnosis of macular disorders and in differentiating retinal from optic nerve disease.[10] This test has not been systematically studied in patients with ischaemic retinal disorders, although sporadic reports have found it to be less sensitive than abnormalities of the scotopic ERG.[5] This simple test, in addition to the ERG b wave recovery time, deserves wider investigation both in the diagnosis of early unilateral low pressure retinopathy and in assessing the response to surgical treatment by revascularisation.[11 12]

We are grateful to Mr Jonathan Robbins and Mrs Janet Turner for assisting in the EOG and ERG recordings and to the Special Trustees of St Thomas's Hospital for financial support.

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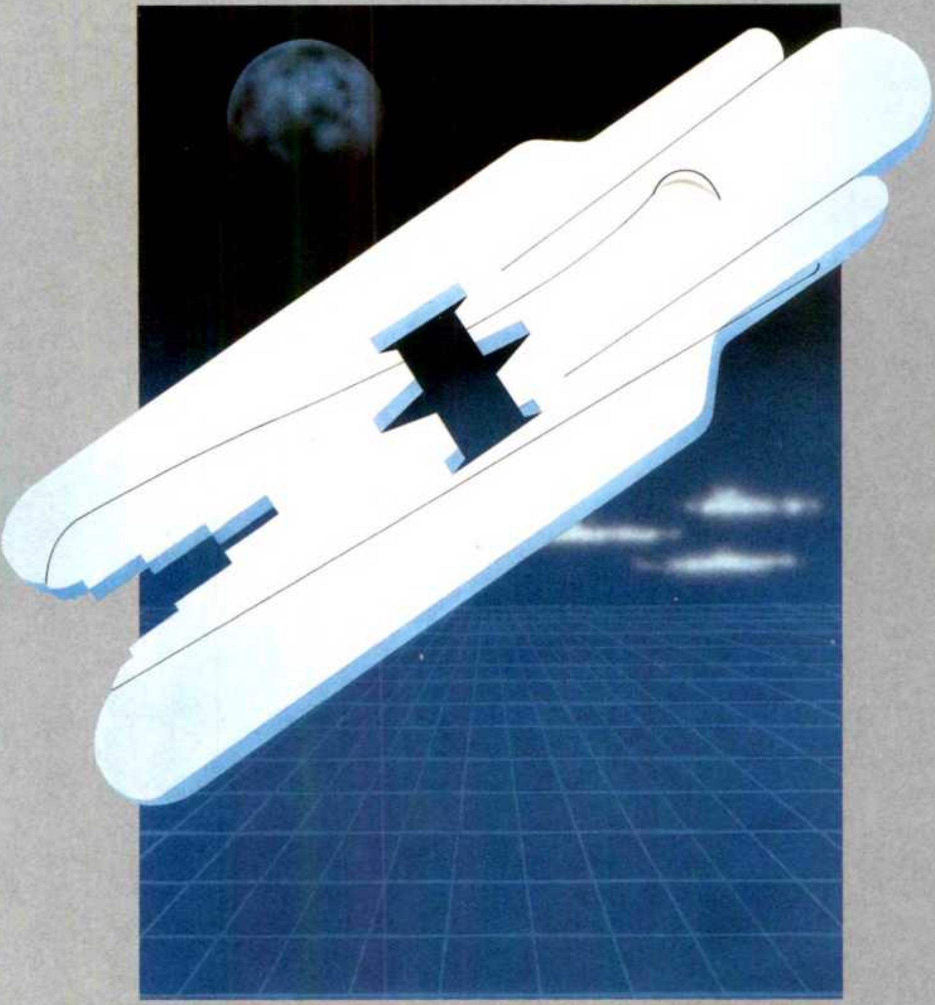

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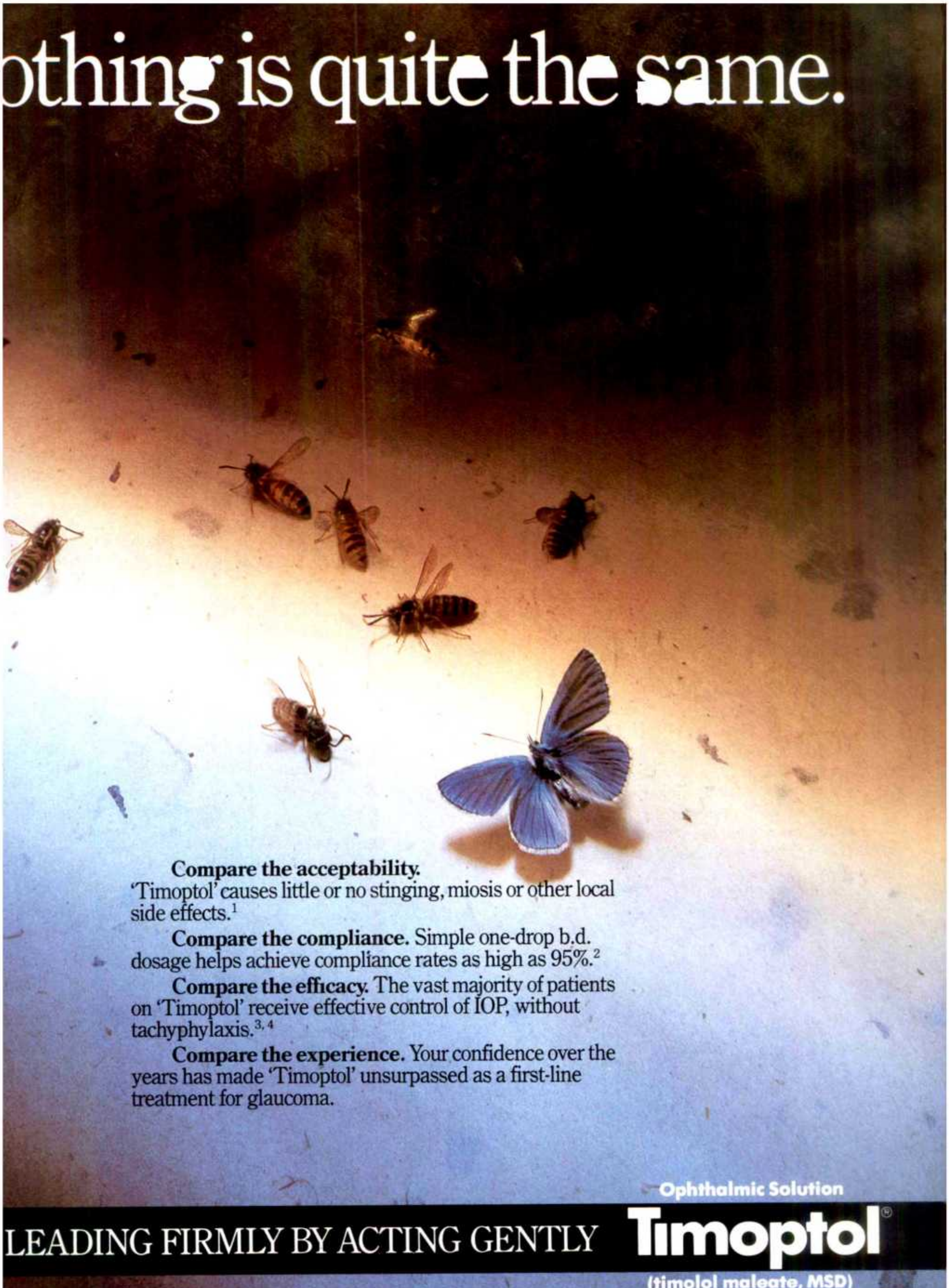

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British Journal of Ophthalmology, 1986, **70**, 657–661

Retinal toxicity of amphotericin B in vitrectomised versus non-vitrectomised eyes

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SUMMARY The retinal toxicity of intravitreally administered amphotericin B was compared in non-vitrectomised versus vitrectomised rabbit eyes. Doses of 5 and 10 μg in both groups resulted in transient vitritis but had no effect on electroretinograms. Histopathological examination four weeks after injection showed vitreous cells and minimal areas of retinal necrosis in both groups at 5 or 10 μg doses. At these doses vitrectomy did not modify the retinotoxic effects of intravitreally administered amphotericin B. At higher doses marked toxicity was found in both vitrectomised and non-vitrectomised groups.

The administration of amphotericin B by direct intravitreal injection is accepted treatment in the management of fungal endophthalmitis, because the drug does not penetrate the vitreous cavity by other modes of administration.[1-6] It is known that retinal toxicity may occur after intravitreal injection of amphotericin B in the rabbit eye.[7 8] Pars plana vitrectomy has also been employed in the management of fungal endophthalmitis.[3-6] However, it is not yet known whether vitrectomy affects the retinal toxicity which may occur after intravitreal amphotericin B injection.

It is possible that vitrectomy could influence the toxicity of amphotericin B injected into the vitreous cavity in different ways. On one hand the removal of vitreous would remove a site for drug binding, and could allow easier drug passage to the retina, allowing one to postulate possible increase in toxicity. On the other hand the disappearance of amphotericin B in vitrectomised rabbit eyes is accelerated in comparison with non-vitrectomised eyes.[9] This would leave less drug in the vitreous cavity to interact with the retina, allowing one to postulate that vitrectomy might result in less retinal toxicity.

The purpose of this study was to evaluate in an animal model whether pars plana vitrectomy has an effect on the ocular toxicity of amphotericin B administered by direct intravitreal injection.

Material and methods

New Zealand albino rabbits weighing 2·5 to 3·5 kg were employed. Anaesthesia was obtained with intramuscularly administered ketamine (30 mg/kg of body weight) and xylazine (5 mg/kg of body weight), 2·0 ml of retrobulbar 2% lignocaine, and topical 0·5% proxymetacaine (proparacaine). Cyclopentolate and phenylephrine were used for mydriasis.

Two groups of rabbits were prepared. (1) *Vitrectomised.* Animals underwent pars plana vitrectomy and lensectomy as described previously,[10] with some modifications. A bent 20-gauge needle was used for infusion during the lensectomy rather than a sutured infusion cannula. Infusion during vitrectomy was accomplished with a Charles infusion sleeve over the 20-gauge suction cutter (Ocutome). A transvitreal endoilluminator was employed. To separate the effects of possible vitrectomy-induced complications from toxic effect due to the drug, animals developing retinal detachments or other pathology during the two weeks after vitrectomy surgery were discarded before entry into the study (two animals). (2) *Non-vitrectomised.* These animals underwent no surgical manipulation.

Amphotericin B (Fungizone) was obtained from a single lot and reconstituted in sterile water immediately prior to use. Within each group of 16 animals four were assigned to intravitreal injection of one of four amphotericin B doses: 5, 10, 50, or 250 μg (in a volume of 0·1 ml). Intravitreal injections were

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performed as previously described.[7] Each animal's paired eye served as a control, receiving the appropriate manipulation (vitrectomy/lensectomy versus non-vitrectomy) for that group, and 0·1 ml of intravitreal balanced salt solution instead of amphotericin. After the injection all eyes were examined by ophthalmoscopy daily during weeks 1 and 2, and then every other day for weeks 3 and 4.

Scotopic electroretinograms were obtained in both groups. The rabbits were preadapted to a background illumination of $3 \cdot 9 \times 10^{-3}$ foot-lamberts for 5 minutes, followed by 12 minutes of dark adaptation. A Burian-Allen contact lens electrode was applied to the cornea, and a ground electrode was placed subdermally in the scalp. An integrated Ganzfeld flash stimulus of 1·07 foot-lambert-seconds was then used, each eye receiving five flashes (Grass PS-2 Photostimulator) at one-minute intervals. Electroretinograms were recorded with internally calibrated preamplifiers (Grass P-511) and a microcomputer. Responses were recorded on a floppy disc.

The A-B ratios were expressed as the ratio of the A-B amplitude (from the trough of the A wave to the peak of the B wave) of the experimental eye to the A-B amplitude of the control eye. Vitrectomised animals had electroretinograms performed before vitrectomy, two weeks after vitrectomy but before intravitreal injection, and four weeks after intravitreal injection. Non-vitrectomised animals had electroretinograms done before intravitreal injection, two weeks after injection, and four weeks after injection. Both eyes of each animal were tested during the same session.[11 12]

Four weeks after amphotericin B injection the animals were killed and both eyes from all animals were enucleated and placed in formalin. Each eye was examined grossly. Routine histological sections were obtained for microscopic examination after the eye was embedded in paraffin. All histological sections were stained with haematoxylin and eosin and were read in masked fashion by an ophthalmic pathologist.

Results

OCULAR EXAMINATIONS

Non-vitrectomised eyes injected with 5 and 10 μg amphotericin B showed no abnormalities except that in six of eight eyes there was mild vitreous haze. This cleared within one week. At 50 μg all eyes developed a moderate vitreous haze persisting for a period of two to three weeks after injection. At 250 μg severe vitreous haze persisting two to three weeks along with moderately dense cataracts developed in three of four eyes. All non-vitrectomised eyes at the 50 and 250 μg dose also developed rhegmatogenous retinal detachments within two weeks of amphotericin B injection (Fig. 1).

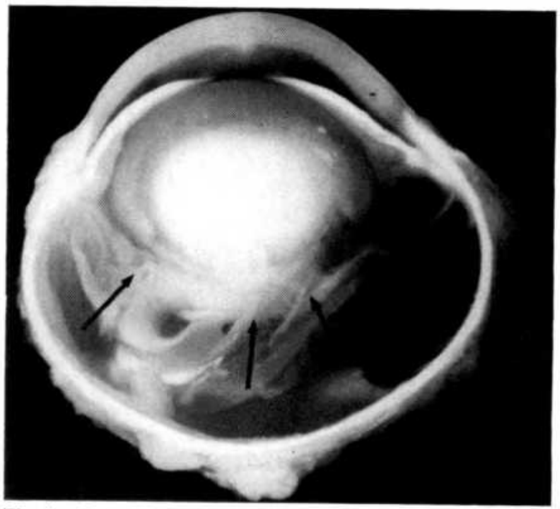

Fig. 1 *Gross section from non-vitrectomised eye four weeks after 250 μg intravitreal amphotericin injection. Note total retinal detachment (arrows), and subretinal haemorrhage.*

The ophthalmological findings in the vitrectomised eyes injected with amphotericin B were similar to those of non-vitrectomised eyes. Mild transient vitreous haze was seen in five of eight eyes at the lower doses (5 and 10 μg). Rhegmatogenous retinal detachments developed in all eyes at the 50 and 250 μg doses. Interestingly, at the higher doses (50 and 250 μg) vitrectomised eyes were noted to have white fibrous-appearing strands within the vitreous cavity. This finding was not evident in non-vitrectomised eyes injected with amphotericin B at the same doses.

Matched control eyes (which received intravitreal balanced salt solution) from both vitrectomised and non-vitrectomised groups did not show any pathological lesions.

ELECTRORETINOGRAPHY

The results of electroretinography are shown in Table 1. The mean A-B ratios of the 5 and 10 μg vitrectomised and non-vitrectomised eyes were similar (with overlap of data points at each concentration), and there was no statistical difference between the groups. At higher drug doses (50 μg and 250 μg), where retinal detachment occurred in all eyes, the groups did differ, since all except one of the vitrectomised eyes had extinguished electroretinograms (Table 1). This effect of vitrectomy at high dose was significant ($p<0 \cdot 01$, Fisher's exact test).

A-B amplitude ratios in vitrectomised animals two weeks after vitrectomy but prior to injection were virtually identical when compared with the same

Table 1 *Ratio of the mean amphotericin injected A-B amplitude to control A-B amplitude*

Dose (micrograms)	*Non-vitrectomised*	*Vitrectomised*
5	0·87 (0·11)	0·94 (0·08)
10	1·04 (0·17)	1·06 (0·15)
50	0·41 (0·21)	<0·01 (—)*
250	0·19 (0·18)	0·01 (0·25)*

*The 50 and 250 μg vitrectomised eyes had A-B ratios approaching zero. To ascertain whether there was any electroretinographic activity at all in these eyes we also used longer adaptation times and increased stimulus intensities. These manipulations did not result in increased responses.

animal's ratio determined before vitrectomy. This indicates that surgery itself did not have an adverse effect on the electroretinogram.

HISTOPATHOLOGY

In both groups at lower drug doses (5 μg and 10 μg) mild vitreous inflammation with an increase of polymorphonuclear leucocytes and lymphocytes was seen (Table 2). Segmental microscopic retinal necrosis was also noted in lower dose vitrectomised and non-vitrectomised eyes (Fig. 2). More extensive retinal necrosis was observed at the 50 and 250 μg concentrations in both groups (Fig. 3). Some of the 50 and 250 μg treated eyes in both groups showed choroiditis with a predominately lymphocytic infiltrate (Table 2). Retinal detachments were noted in all eyes of both groups receiving 50 or 250 μg (Fig. 1). Prominent fibrogliotic periretinal tissue was noted histopathologically in the higher dose (50 and 250 μg) vitrectomised group eyes (Fig. 4), but not in the similarly treated non-vitrectomised eyes. Fibrogliotic elements were sometimes noted to exert tractional forces on the retina. At histopathological examination only the amphotericin treated vitrectomised eyes showed periretinal proliferations.

Table 2 *Histopathology four weeks after intravitreal amphotericin B injection*

	Amphotericin dose							
	5 μg		*10 μg*		*50 μg*		*250 μg*	
	NV	*V*	*NV*	*V*	*NV*	*V*	*NV*	*V*
Number of eyes	4	4	4	4	4	4	4	4
Vitritis	3	2	3	3	4	3	4	3
Choroiditis	0	0	0	0	2	2	3	2
Retinal detachment	0	0	0	0	4	4	4	4
Microscopic retinal necrosis	3	3	3	3	4	4	4	4
Cyclitic membrane	0	0	0	0	0	0	1	0

V=vitrectomised eye. NV=non-vitrectomised eye.

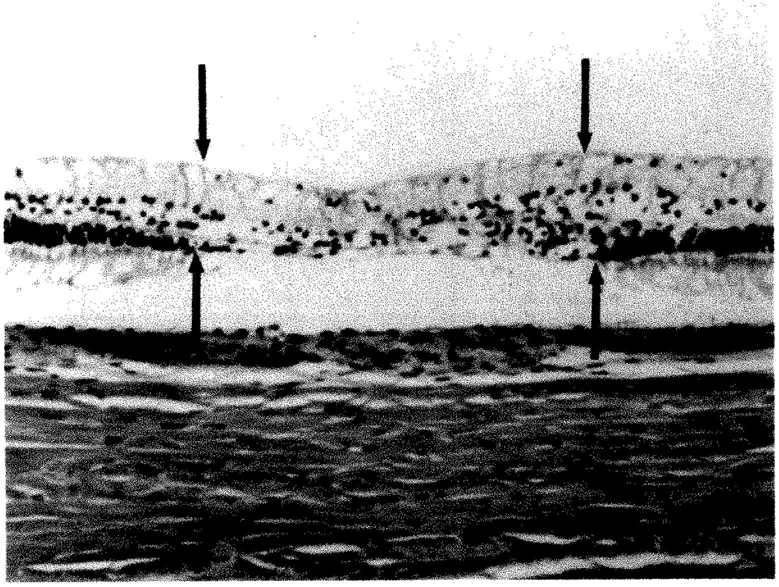

Fig. 2 *Segmental area of retinal necrosis (between arrows) with normal adjacent retina, seen in 5 μg non-vitrectomised eye four weeks after injection of amphotericin. Similar findings were noted in both 5 and 10 μg vitrectomised and non-vitrectomised groups. Retinal detachment is artefactual. (Haematoxylin-eosin, ×350).*

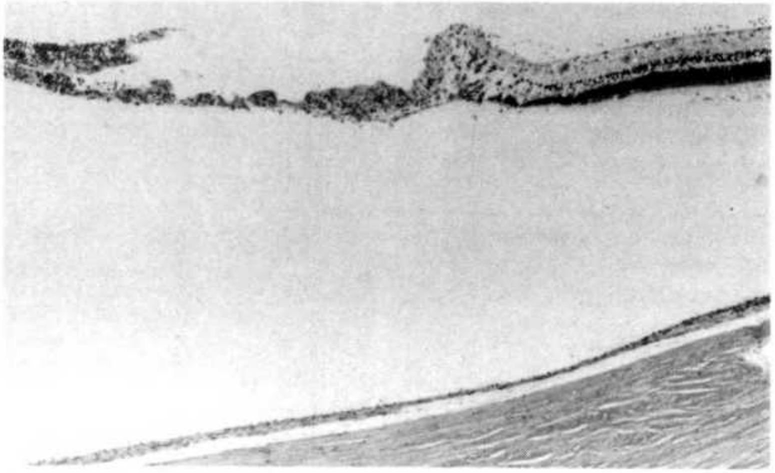

Fig. 3 *More extensive full thickness retinal necrosis with normal adjacent retina seen in 50 μg non-vitrectomised eyes four weeks after injection. Similar findings noted in both 50 and 250 μg non-vitrectomised and vitrectomised eyes. (Haematoxylin-eosin, ×200).*

Discussion

Although the use of intravitreal antibiotics is becoming an accepted form of treatment for endophthalmitis, the role of pars plana vitrectomy in the therapy of these infections is not clearly defined. Therapeutic vitrectomy seems logical, allowing incision and drainage to remove the bulk of infectious organisms and associated inflammatory debris. Cottingham and Forster[13] have shown in a rabbit model of bacterial

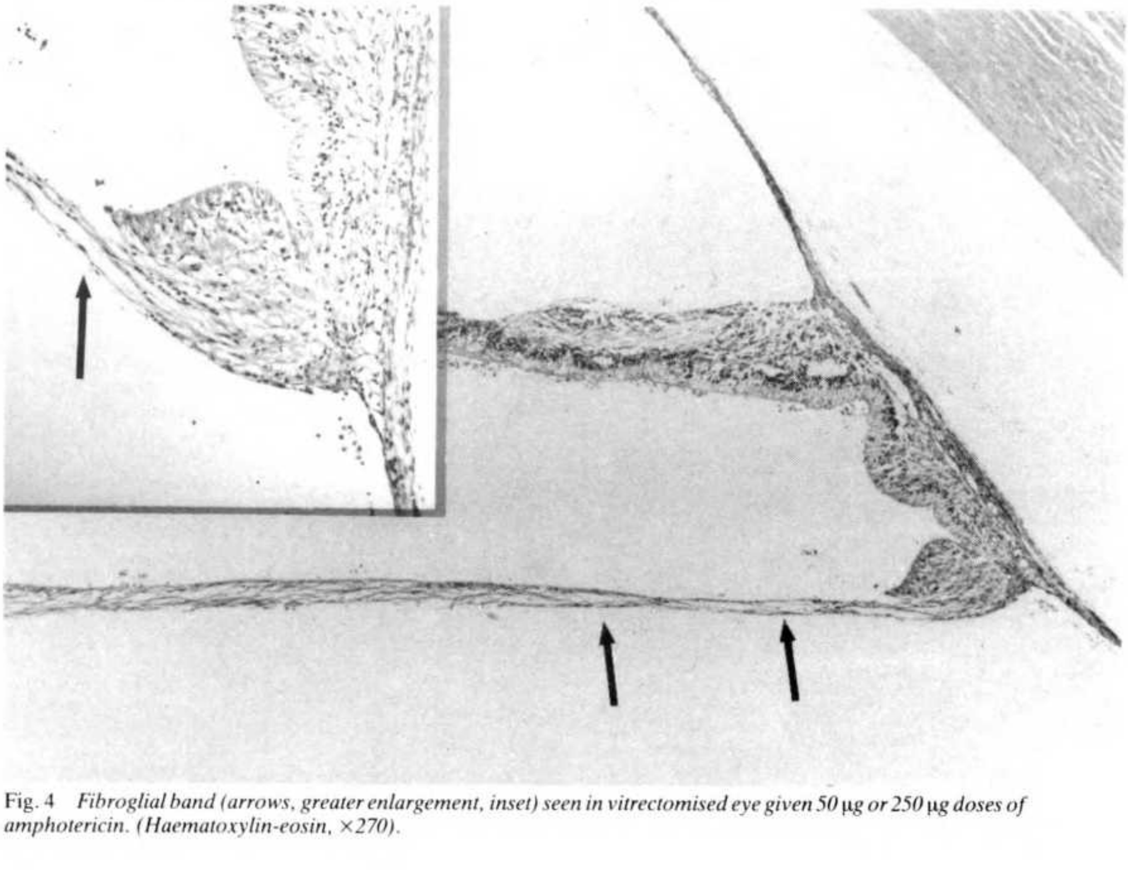

Fig. 4 *Fibroglial band (arrows, greater enlargement, inset) seen in vitrectomised eye given 50 μg or 250 μg doses of amphotericin. (Haematoxylin-eosin, ×270).*

endophthalmitis that eyes treated with combined vitrectomy and intraocular antibiotics had a greater number of negative cultures at one week than if treated with intraocular antibiotics alone.

Previous studies have been performed to assess retinal toxicity after direct intravitreal injection of amphotericin in the rabbit model. However, to our knowledge data from controlled studies regarding retinal toxicity in vitrectomised compared with non-vitrectomised eyes has not previously been reported. One study has looked at the effect of intravitreally administered amphotericin B after vitrectomy, but that study did not employ non-vitrectomised controls.[14] That study did not demonstrate toxicity of intravitreal amphotericin at doses of 5 µg or less. Another study looked at the toxicity of amphotericin B methyl ester administered in vitrectomy infusion fluid.[15] In that study the maximum non-toxic dose of the methyl ester in the vitreous infusion fluid was 75 µg/ml. However, that is not analogous to regimens in which vitrectomy is followed by isolated intravitreal amphotericin B injections.

A previous study concerning clearance of amphotericin after intravitreal injection shows that eyes that had undergone vitrectomy/lensectomy cleared amphotericin much more rapidly than non-vitrectomised eyes or eyes which had had lensectomy alone.[9]

Our data indicate that only minimal retinal toxicity develops at 5 and 10 µg doses of amphotericin in both vitrectomised and non-vitrectomised eyes. Except for transient vitritis and small skip areas of retinal necrosis seen histopathologically, these eyes appeared normal, and electroretinogram A-B amplitude ratios were unaffected. Thus vitrectomy does not appear to increase the degree of retinal toxicity from amphotericin at doses employed clinically. However, at the 50 and 250 µg concentrations marked retinal toxicity was apparent clinically, electroretinographically, and histopathologically in both vitrectomised and non-vitrectomised eyes. At these highly toxic dose levels electroretinogram effects were found to be more marked in vitrectomised eyes than in non-vitrectomised eyes. We are unable to explain this statistically significant finding, since retinal detachments were present in all eyes of both groups at these dose levels.

The data presented in this study demonstrate that vitrectomy makes the eye neither more susceptible nor less susceptible to toxic effects of intravitreal amphotericin at doses commonly employed clinically. However, the extent to which these data obtained in an animal model applies to humans is unknown.

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Ocular histopathology of acrodermatitis enteropathica

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SUMMARY Acrodermatitis enteropathica is the clinical expression of congenital zinc deficiency and is now treated with supplemental zinc. This report details the ocular histopathology of a child who died before efficacious treatment was available. The findings include corneal epithelial thinning and loss of polarity, anterior corneal scarring and loss of Bowman's membrane, cataract formation, ciliary body atrophy, retinal degeneration, RPE depigmentation, and optic atrophy.

Acrodermatitis enteropathica (AE) is a rare hereditary abnormality of zinc metabolism which usually presents early in infancy, often after weaning from breast milk. Untreated, the disease follows a fluctuating course characterised by bullous pustular dermatitis of the extremities and about the body orifices, chronic diarrhoea associated with malabsorption and failure to thrive, central nervous system abnormalities, and impaired immune function with frequent infections.[1 2] The dermatitis frequently involves the lateral canthal area and lids as a vesico-bullous eruption evolving into a psoriasiform reaction. The cilia of the brow and lid margin may be lost following the onset of the dermatitis. Conjunctivitis frequently accompanies the dermatitis.[3 4] Linear subepithelial corneal opacities are occasionally found during exacerbations of the dermatitis.[5] Cataracts, optic atrophy, and punctal stenosis have also been reported in patients with acrodermatitis enteropathica.[4 6]

Initially human breast milk and antibiotic therapy produced a modest improvement in this disease. In 1953 diiodohydroxyquinolone therapy was accidentally found to be efficacious. The mechanism of action of the drug was not known at the time, but it has recently been shown that the drug augments intestinal zinc absorption. In 1973 Moynahan and Barnes[7] recognised zinc deficiency as the basic defect in the disease process and successfully reversed all the clinical signs and symptoms with supplemental zinc sulphate alone. Oral zinc supplementation is the current mode of therapy.

The case described here was discovered during a larger study of the ocular effects from all causes of zinc deficiency. The case was managed entirely between 1965 and 1971, four years before the discovery of the basic defect and effective treatment of AE. The disease was ultimately fatal in this case. Both eyes were obtained at necropsy for histological study. Except for a report of a corneal biopsy,[5] there have been no previous reports of the ocular histology in this disease.

Case report

This male child was an 8 pound 9 ounce (3884 g) product of an uncomplicated, full term pregnancy. He was in good health until age 1 month when he developed a blistering skin rash on his cheeks. The rash spread to involve the skin around the eyes, nose, and mouth. By the end of two months skin lesions were also noted on the abdomen and extremities. At 3 months he developed diarrhoea and failure to thrive. A skin biopsy at that time showed parakeratosis typical of acrodermatitis enteropathica (Fig. 1). The association between zinc deficiency and AE had not been made at that time (1965), so the patient was treated over the next six years with intermittent courses of broad spectrum antibiotics, breast milk, and diodoquin. He partially responded to these modes of therapy but nevertheless developed total alopecia, intermittent acrodermatitis, and intermittent diarrhoea with suboptimal weight gain. Spasticity attributed to central nervous system involvement by the AE had developed by 8 months of age. The child suffered several episodes of cardiopulmonary arrest at 11 months. Because of lack of co-ordination of his vocal cords, a tracheostomy was required, which

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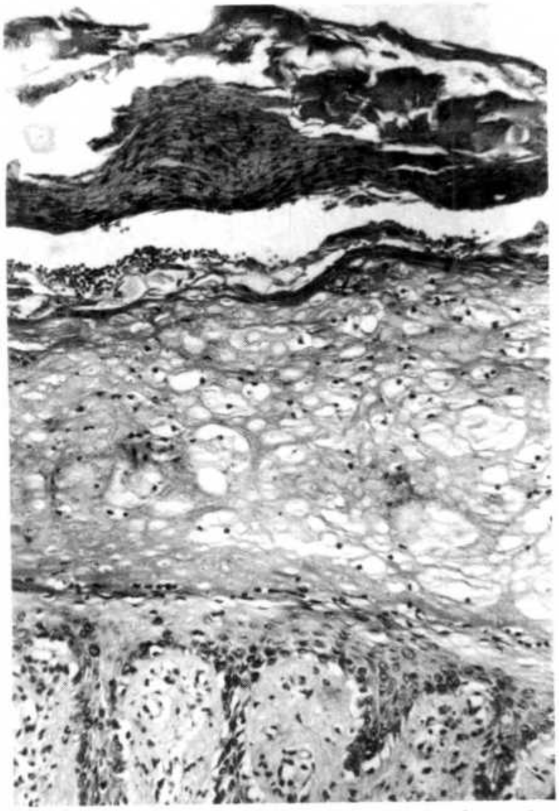

Fig. 1 *Skin biopsy showing hyperkeratosis, parakeratosis, and acanthosis. (Haematoxylin and eosin, ×16).*

remained in place for one year. By age 18 months the child developed searching nystagmus associated with bilateral optic atrophy and slight attenuation of retinal vessels as well as signs of psychomotor retardation. Bilateral keratoconjunctivitis was noted, and this recurred concomitantly with the skin rash during the subsequent years. A second skin biopsy performed at age 3 again showed parakeratosis typical for AE. While the child was in hospital at age 4 for an episode of severe skin rash and diarrhoea, bilateral gross anterior corneal opacities were seen which had completely resolved by the time he was re-examined at age five. Bilateral severe blepharoconjunctivitis and bilateral anterior corneal vascularisation had developed by the time of his final ocular examination at age 7.

The patient's entire course was complicated by frequent infections including otitis media, urinary tract infections, and skin infections. He died in 1971 (age 7) because of Gram-negative bacterial sepsis presumed to have originated in the perianal area. A necropsy was performed. Pertinent findings at post-mortem examination were the skin lesions typical of acrodermatitis enteropathica, absence of thymic tissue, marked degeneration of the optic nerves, chiasm, and optic tracts and extensive cerebellar degeneration. Both eyes were removed for histological examination.

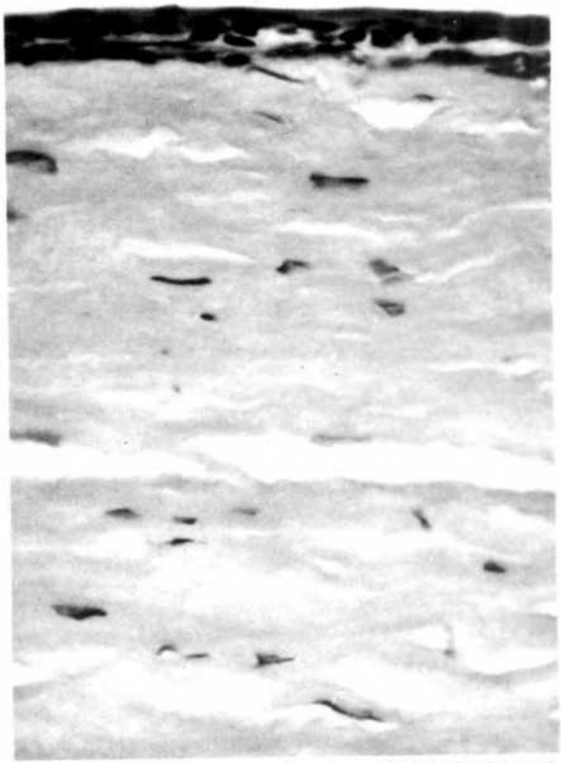

Fig. 2 *Section of the cornea showing epithelial thinning and loss of polarity as well as anterior stromal scarring and loss of Bowman's membrane. (Haematoxylin and eosin, ×31).*

PATHOLOGY OF EYES

The right and left eyes were similar in appearance. They each measured 18×18×18 mm with the optic nerve cut flush to the globe. The corneas were translucent and the optic discs were pale. The remaining structures of both globes appeared normal. Both globes were processed for paraffin embedding.

New sections were cut from the existing paraffin blocks and original sections containing the optic disc were restained.

Both eyes had a similar microscopic appearance. The corneal epithelium was reduced in thickness to one to three cell layers of flattened squamous epithelial cells over the entire surface of the cornea (Fig. 2). All polarity of the epithelium was lost. Bowman's

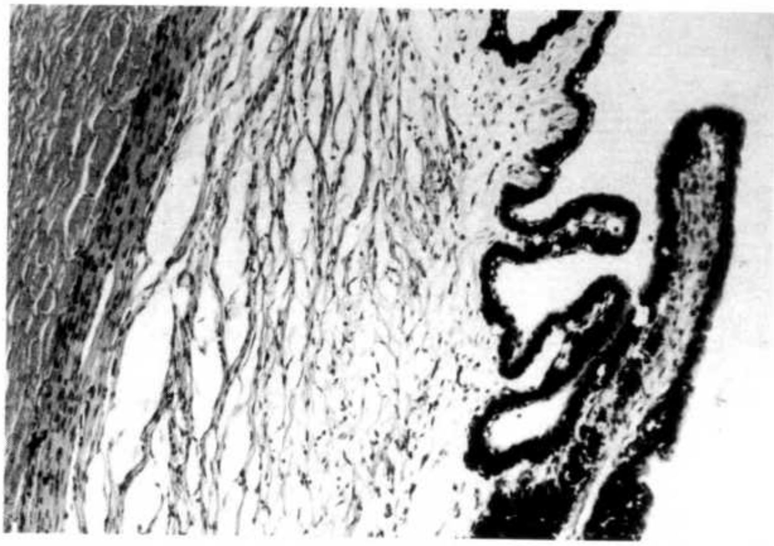

Fig. 3 *Section of the ciliary body showing extensive loss of the circular and oblique muscle fibres. (Haematoxylin and eosin, ×6·2).*

membrane could be identified only in the periphery of the right cornea. No Bowman's membrane could be identified in the left cornea. Neither degenerative nor inflammatory pannus could be identified in either eye. Corneal stroma, Descemet's membrane, and corneal endothelium were unremarkable. The anterior chamber angle structures and iris were normal. There was extensive atrophy of the circular and oblique muscles of the ciliary body (Fig. 3). The longitudinal muscle bundle appeared intact. There was some posterior migration of lens capsular epithelium and early cortical degenerative changes (Fig. 4). The choroid was normal and the choriocapillaris was well preserved.

There appeared to be extensive degeneration of the retinal pigment epithelium throughout the posterior pole (Fig. 5), with relatively normal appearing pigment density in the periphery (Fig. 6). The retina was attached and showed mild autolytic changes throughout. There was some preservation of rod and cone outer segments in the posterior pole; however, these structures were completely lost anterior to the equator. There was extensive loss of the ganglion cell and nerve fibre layers of both eyes, and nearly complete atrophy of the disc and adjacent optic nerve (Fig. 7). There did not appear to be any extensive posterior bowing of the lamina cribrosa of the left eye. The central area of the optic nerve of the right eye was not represented in the sections available. The sclera was of normal calibre throughout.

Discussion

Zinc is an essential trace element which is necessary for RNA and DNA synthesis and the function of a

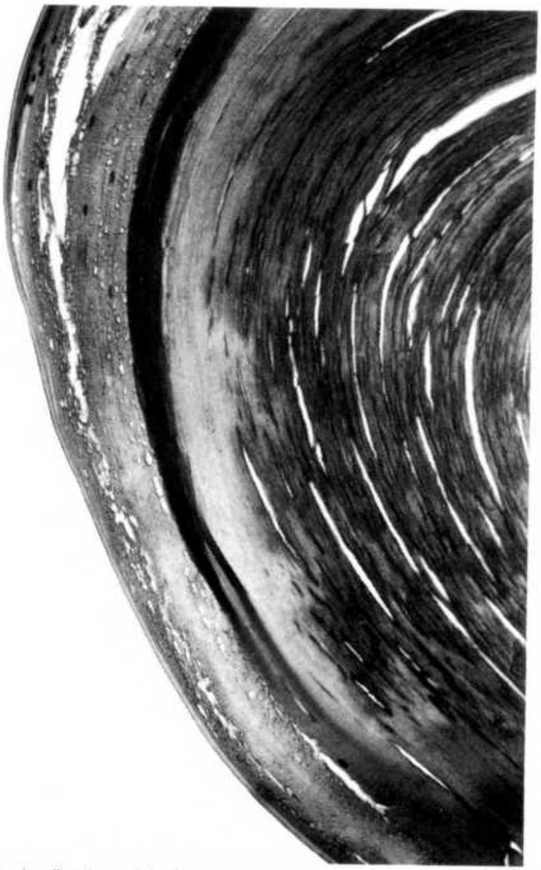

Fig. 4 *Section of the lens showing early posterior migration of the lens epithelium and early cortical degenerative changes. (Periodic acid-Schiff, ×17).*

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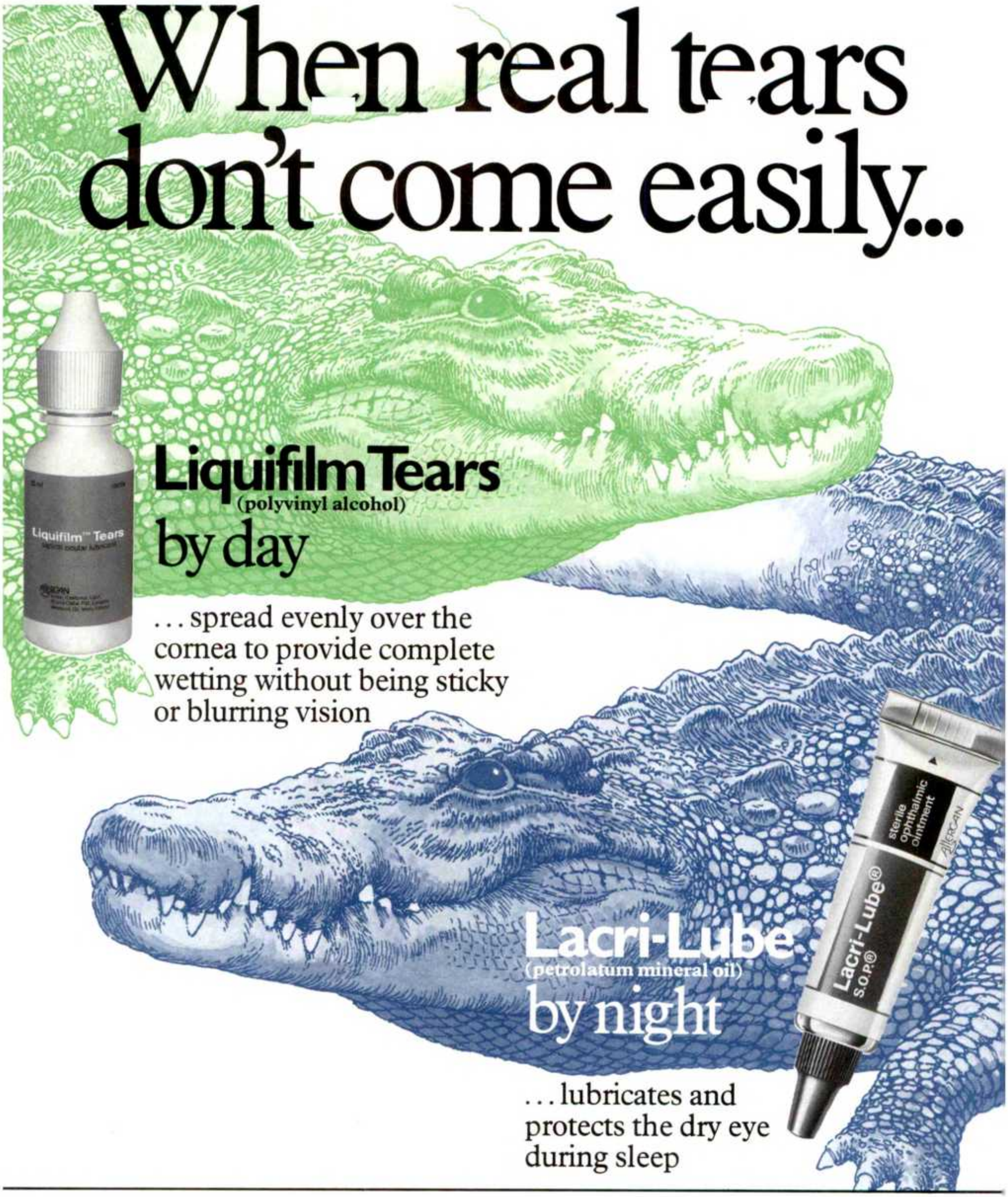
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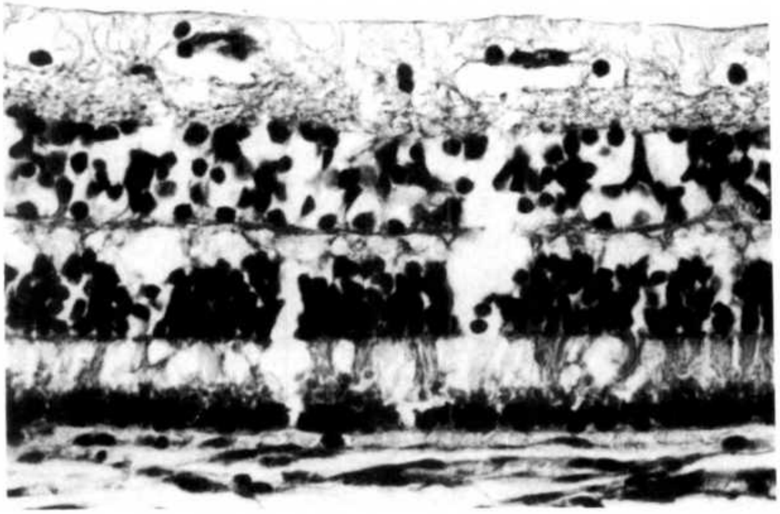

Fig. 5 *Section of the posterior retina showing atrophy of the inner and outer retinal layers associated with a decreased density of the retinal pigment epithelium and preservation of the choriocapillaris. (Haematoxylin and eosin, ×25).*

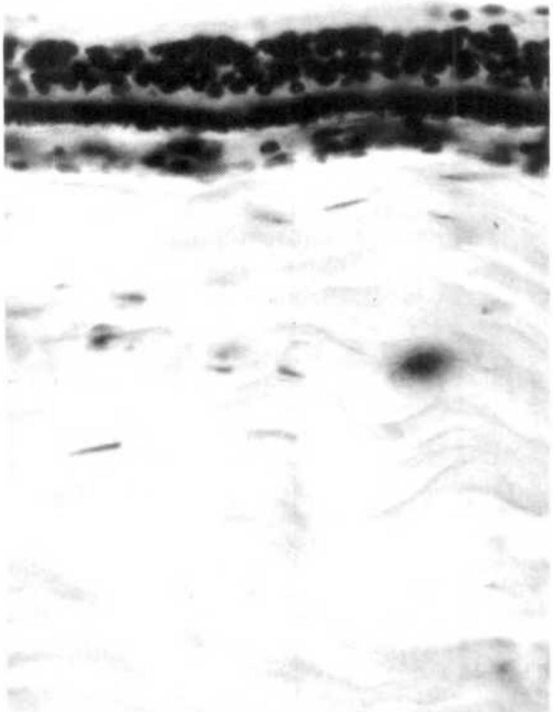

Fig. 6 *Section of the peripheral retina showing severe atrophy of the neurosensory retina but near normal neuroectodermal pigment density of the retinal pigment epithelium. (Haematoxylin and eosin, ×31).*

variety of zinc metalloenzymes.[8] Much of the knowledge of the metabolic role of zinc has been derived from the manifestations of zinc deficiency such as acrodermatitis type skin lesions, diarrhoea with malabsorption, growth retardation, hypogonadism, anorexia with abnormalities of taste and smell, impaired wound healing, alterations in vitamin A metabolism and retinal dysfunction, impaired immune function, and teratogenesis.[8-17] A variety of processes or disease states have now been identified in which zinc deficiency may occur, including alcoholism with or without liver disease, regional enteritis, sprue, short bowel syndrome, sickle cell anaemia, certain types of cancer, pregnancy, total parenteral nutrition (TPN), as well as the congenital form, acrodermatitis enteropathica.[7 11 18-22]

The onset of the case presented here was characterised by the dermatitis of zinc deficiency. One aetiological factor for the dermatitis appears to be a marked alteration of amino acid metabolism, which is essential in cell renewal and repair processes of the integument.[23] The distribution of the skin lesions has not been explained. It has been suggested that persistent mechanical or chemical trauma to the areas of involvement may be partially responsible.[24] If this is true, the repeated chemical trauma of increased tear production associated with nonspecific conjunctivitis may lead to the acrodermatitis of the lateral canthal area.

The child then developed severe diarrhoea and later developed manifestations of severe psychomotor retardation. The exact mechanism of these expressions of the disease has not yet been adequately explained.

Impaired cellular immunity and thymic atrophy

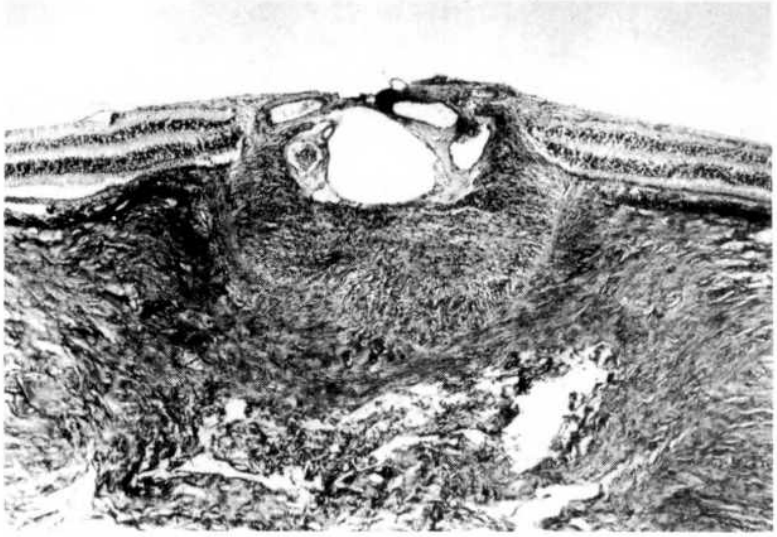

Fig. 7 *Section of the peripheral optic disc showing extensive atrophy. (Haematoxylin and eosin, ×1·5).*

have been found in both experimental animals and humans with zinc deficiency.[16] These findings may help to explain the child's frequent infections of the skin, middle ear, and urinary tract throughout his life.

Some of the highest concentrations of zinc in the body are found in the ocular tissues, yet the exact role of zinc in the eye is as yet ill defined.[25] The high turnover rate of the cells of the corneal epithelium appears to place them at the same risk of abnormality as the skin epithelium at the mucocutaneous junction and acral areas. The structural expression of this appears to be the thinning and loss of polarity seen in the corneal epithelium. The repeated trauma associated with the conjunctivitis and blepharitis of the disease to this already compromised epithelium probably explains the loss of Bowman's membrane and subsequent anterior corneal scarring. The transient corneal opacity seen clinically during severe exacerbation was most likely a gross manifestation of the scarring process which subsequently healed to a point where it was no longer clinically apparent.

Two metalloenzymes which are essential to ocular function are zinc dependent. They are alcohol dehydrogenase, which is active in converting retinol, the circulating form of vitamin A, to retinal, the form necessary for rhodopsin production, and carbonic anhydrase, which functions in aqueous production.[8]

Abnormalities in retinal function in humans, specifically impairment of dark adaptation, have been reported during episodes of zinc deficiency.[18,19] Structural abnormalities in zinc deficient rats included a degeneration of the retinal pigment epithelium and disorganisation of the photoreceptor outer segments.[26,27] In this case, although some autolysis was present, there was evidence of depigmentation of the retinal pigment epithelium posteriorly and a loss of photoreceptor outer segments out of proportion to the degree of autolysis present.

Apparently because of the degree of psychomotor retardation, this child was very difficult to examine, and the intraocular pressure was never recorded. There was no clinical or histological evidence of increased or decreased intraocular pressure. The extreme atrophy of the circular and oblique muscles of the ciliary body at the site of presumed carbonic anhydrase activity may suggest a relationship, though nothing can be proved.

The optic atrophy in this case was profound, which is somewhat unusual in acrodermatitis enteropathica. Because of the degree of cerebellar atrophy, this may have been a part of a more generalised central nervous system involvement. It is also possible that the episodes of cardiopulmonary arrest several months prior to the clinical manifestation of the optic atrophy may have had a role.

The biochemical defect leading to cataract in zinc deficiency has not yet been found. The lens changes in this case appear to be early senile changes. No posterior subcapsular lens changes were found.

Although acrodermatitis enteropathica is now treatable and such a severe ocular expression of the disease may not again be seen, it is extremely important to recognise the early manifestations of this congenital disease so that treatment can be instituted promptly. It is also important to recognise that the ocular manifestations of zinc deficiency seen in acrodermatitis enteropathica may arise in many other, more common, diseases complicated by zinc deficiency.

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Measurement method of the anterior chamber volume by image analysis

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SUMMARY A new computerised method of measurement of the anterior chamber in the human eye is described. Photographs of the anterior chamber were taken with a Zeiss slit-lamp 75-SL and converted from an optical image into a true image by computer with a digitiser. We obtained data on both the anterior chamber volume and also the anterior chamber depth, peripheral anterior chamber volume, the diameter of the anterior chamber, and the degree of the iridocorneal angle. These data were simultaneously displayed several seconds after in-put by the digitiser. In mensuration by digitiser on three occasions from a single photograph of a given eye the mean deviation rate was about 0·7%, and the mean deviation rate of 10 successive exposures of one eye was 3·5%. By this image analysis technique an accurate profile of the anterior chamber is displayed of the pupil margin, iris-root insertion, and central anteroposterior pupillary axis. These data help us to understand the mechanism of primary angle-closure glaucoma.

Methods of measuring the anterior chamber volume have been described. But they have been somewhat difficult to apply in clinical examination and have not been sufficiently perfected to be useful in an outpatient setting. Recently Johnson *et al.*[1] reported on a new simple method for measuring the anterior chamber volume, in which they used an unaltered, commercially available slit-lamp camera system. In this method the anterior chamber volume is calculated from the anterior chamber scale obtained from a plastic model eye together with a transparent optically distorted grid overlay.

We have developed another convenient method of measuring the anterior chamber volume. It is a new computerised method for converting the optically distorted image into a true image and for calculating the volume from the true dimensions. We can furthermore obtain a true profile of the anterior chamber such as pupil margin and iris root insertion. The true profile provides data for comparing normal eyes with glaucomatous eyes.

The purpose of this report is, first, to describe our new simplified optical method for measuring the anterior chamber volume and for providing a diagram of the anterior chamber profile by means of a computer with a digitiser. Secondly, we discuss the accuracy of the values obtained by this method.

Materials and methods

The profile of the anterior eye segment was photographed with Zeiss slit-lamp 75-SL. The vertical slit-beam was projected along the visual axis of the eye, and the camera was locked at an angle of 45° to the left for the slit-lamp with the use of the longest slit. Shutter speed was 1/60 second, photoadapter 14, flash impulse 4, zoom factor 1·0, illumination of the background 25%, width of the slit-beam 0·1, film Kodak (ASA 400).

The colour photographs, developed and enlarged, were analysed by a digitiser, and the optical image of the anterior eye segment was converted into the true image by computer. A given point (x_i, y_i) was converted into the point (x_r, y_r) in the true image according to the following equations:

$$
\begin{aligned}
r_i &= \sqrt{x^2_i + y^2_i} \\
\zeta_i &= \arctan\,(y_i/x_i) \\
\vartheta &= \arcsin\,(r_i/r_i) \\
\vartheta' &= \arcsin\,(\sin\vartheta/n) \\
r &= \frac{r_k \cdot \sin\vartheta - r_k \cos\vartheta \cdot \tan\,(\vartheta-\vartheta')}{1-\sin\zeta_i \cdot \tan\,(\vartheta-\vartheta')} \\
Z &= r\sin\zeta_i \\
X &= r\cos\zeta_i \\
Y &= r\sin\zeta_i \\
X_r &= x \\
Y_r &= \sqrt{y^2+Z^2}
\end{aligned}
$$

where

x_i is the distance from the axis in the optical image,
y_i is the height at the x_i point in the anterior chamber

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in the optical image, r_i is the distance from the centre of the true corneal radius to the point (x_i, y_i) in the polar co-ordinate, and r is the true distance of r_i, and r_k is the true corneal radius, n is the refractive power of aqueous humor, x_r is the distance from the optic axis in the true image, y_r is the height at the x_r point in the true image, the x axis is set in the vertical plane, the y axis is set in the horizontal plane, the z axis is set in the rectangular plane to the x-y plane, x_r is set in the vertical axis and y_r is set in the optic axis in the true image, and r is the true distance of r_i, ζ_i is the angle in the polar co-ordinate between the x axis and the line from the point (x_i, y_i) to the centre of the corneal radius, ϑ is the angle of incidence, and ϑ' is the angle of refraction.

The true depth of the anterior chamber at intervals of about 0·5 mm from the optic axis of the eye to the iridocorneal angle is read directly from the photograph by a digitiser. According to the method of estimation of the anterior chamber volume described by Johnson *et al.*[1] the anterior chamber volume was assumed to be equal to the volume of revolution of its central sagittal section rotated 180° about the optic axis. The volume of such a solid can be approximated from the sums of the volumes of a series of concentric right circular cylinders, the heights of which are equal to the anterior chamber depths at each of a series of intervals. The upper half and the lower half of the anterior chamber were estimated separately in the present study. Each anterior chamber depth measurement multiplied by computer gives the volume of one of a series of concentric half cylindrical sleeves, the sums of which equal half an anterior chamber volume. The anterior chamber volume consists of the sums of each half of the upper part and the lower part (Fig. 1). These steps can be quickly carried out with the aid of a computer, and, in addition to the data of the anterior chamber volume, several kinds of data such as the peripheral anterior chamber volume, the anterior chamber depth, the diameter of the anterior chamber, the degree of the iridocorneal angle, and the true profile of the anterior chamber are displayed within several seconds (Fig. 2).

The magnification rate was evaluated by a micrometer disc (Zeiss) fixed on the pointer of the fixation

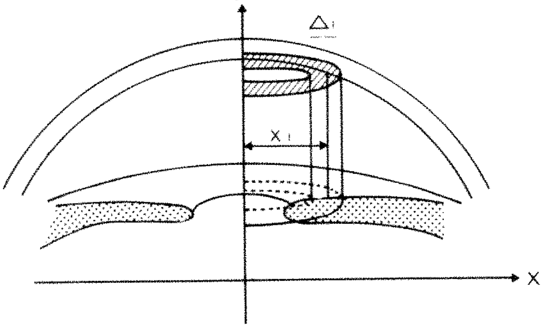

Fig. 1 *The upper half and the lower half of the anterior chamber were estimated separately. The anterior chamber volume consists of the sums of each half of the upper part and the lower part, consisting of a series of concentric half cylindrical sleeves.*[7]

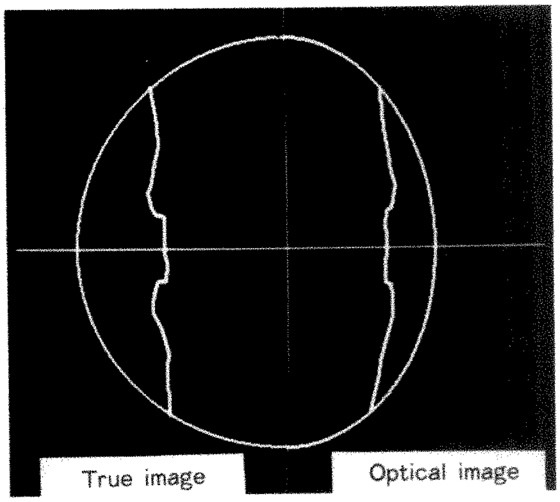

Fig. 2 *The true profile of the anterior chamber was displayed by converting from the optical image to the true image by the computer after input with a digitiser. The true image is displayed on the left side, the optical image on the right.*

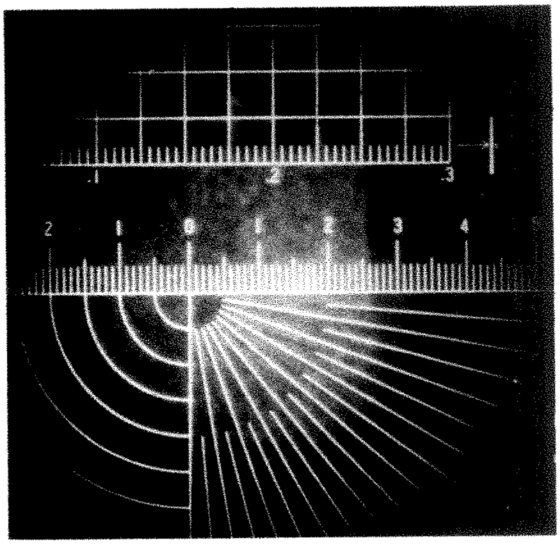

Fig. 3 *The picture of a micrometer disc (Zeiss). The unit of length is 0·01 mm.*

light. The micrometer disc (units of 0·01 mm) was photographed on to the film for the anterior segment of the eye (Fig. 3).

We used a PC-9801F (Nihon Electronic Co.) computer and a Gradimate-SQ-3000 (Oskon Denshi) digitiser for our study.

Our method has been developed from the following assumptions. The corneal surface is spherical with a radius of r_k. The refractive indices of the cornea and the aqueous humour are equal. The thickness of the cornea is 0·6 mm over the entire surface of the cornea. The interval between x_i and x_{i+1} on the iris surface or the lens surface is linear. And the true image of the iridocorneal angle is estimated as the part surrounding both the corneal curvature and the straight line along the iris surface beside the iridocorneal angle.

Results

The consistency of the mensuration procedure was examined by making three estimates of the volume from a single photograph on separate occasions. The results are shown in Table 1.

The consistency of the photographic technique and mensuration procedure with a digitiser was examined by taking 10 exposures of one eye and reading the photograph with a digitiser. The results are shown in Table 2.

Table 1 *Volume of anterior chamber of a subject by mensuration on three occasions from a single photograph of the eye*

Experiment	*1*	*2*	*3*
Volume (μl)	195·6	198·8	196·8

Mean deviation = 1·32 μl (0·7%).

Table 2 *Volume of anterior chamber of a subject obtained from 10 successive photographs*

Experiment	*Volume (μl)*
1	139·6
2	138·7
3	138·1
4	151·1
5	151·4
6	140·0
7	146·0
8	139·3
9	149·7
10	145·7

Mean deviation = 5·04 μl (3·5%).

Discussion

Several methods for measuring the anterior chamber volume from a slit-image photograph have been described.[1-7] Each method preceding that of Johnson *et al.*[1] requires special equipment, with slit-lamp modification. Johnson *et al.*[1] recently reported on a simple optical method for measuring the anterior chamber volume by means of an unmodified, commercially available slit-lamp system and transparent anterior chamber scales. We have developed a new method of measuring the anterior chamber volume. It is an image analysis method for conversion of the optically distorted image into a true image and for calculation of the volume from the dimensions by computer with a digitiser. Both steps are simultaneously carried out by a commercially available computer with a digitiser, and the entire mensuration procedure takes less than 10 seconds. Our method requires neither special equipment nor modification of a standard slit-lamp system. From the distorted image given by a slit-lamp photograph a correctly dimensioned outline of the cross section of the anterior chamber is derived, point by point, by means of a digitiser. This method allows the anterior chamber volume to be derived rapidly from the true image of the anterior chamber, and it also allows the peripheral anterior chamber volume, the anterior chamber depth, the peripheral anterior chamber depth, the diameter of the anterior chamber, and the degree of the iridocorneal angle to be derived at the same time. Furthermore this method provides an estimate of the profile of the anterior chamber—that is, the relative positions of pupil margin, lens surface, iris root insertion, and anteroposterior lens axis.

Although Heim[2] pointed out that it is generally impossible to obtain a view of both angles of the anterior chamber together with vertical slit-beam, fortunately the Zeiss slit-lamp 75-SL has a long enough slit-beam to obtain a view of both angles even with the vertical slit-beam, unlike other slit-lamps. This enabled us to photograph the anterior chamber with the vertical slit-beam. In addition the vertical slit-beam has the advantage of making the measurement accurately, because the width of the anterior chamber angle does not seem to be equal in different sections of the chamber, while there is a great difference between upper half anterior chamber volume and lower half. We recommend the evaluation of data of the anterior chamber volume using the sums of the values of both the upper half and the lower half.

Nagataki *et al.*[8] recently reported on a modified method for calculating the anterior chamber volume. The advantage of this method is that the true anterior chamber dimensions can be measured in an eye of any corneal curvature. By using a digitiser we can also apply this method of measurement to the cases of

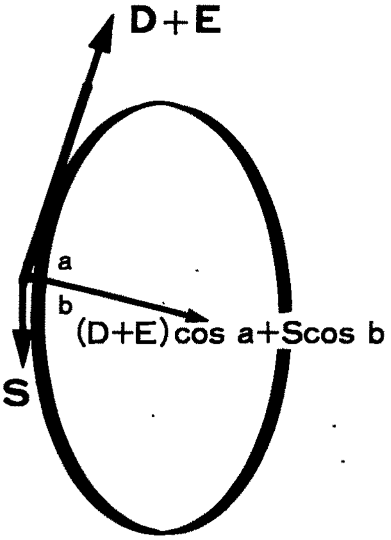

Fig. 4 *Pupil blocking force* (F) *consists of* (D+E) cos a+S cos b. *where* D *is pupil dilating force.* E *is iris-stretching force.* S *is sphincter contracting force.*

radius of the corneal curvature, without the transparent anterior chamber scales reported by Johnson *et al.*[1]

The most important point for maintaining the accuracy of measurement in the photogrammetric method is the precise evaluation of the magnification ratio of the pictures. We fixed a micrometer disc on the fixation pointer to ensure that a constant distance was maintained between the camera and the top of the cornea. This method is particularly accurate for estimating the magnification ratio, because the micrometer disc is photographed on to the film of the anterior chamber. Each photograph was enlarged 5–6 times in the present study. In using a large magnification we reduce the mensuration errors of the digitiser. Using one photograph of a given specimen we tested the mensuration by digitiser three times, and obtained a mean deviation of about 0·7%. This suggests that the mensuration procedure by digitiser is not a substantial source of error.

Another important point during the taking of photographs is the centring of the slit-beam against the cornea. Small errors in alignment of the centre of the slit-beam with the optic axis of the eye are bound to occur.[3,9] In our studies the mean deviation of 10 successive exposures of one eye was 3·5%. Successively exposed pictures, except for those with misalignment of the centre of the slit-beam, should be selected for the estimation of the anterior chamber volume.

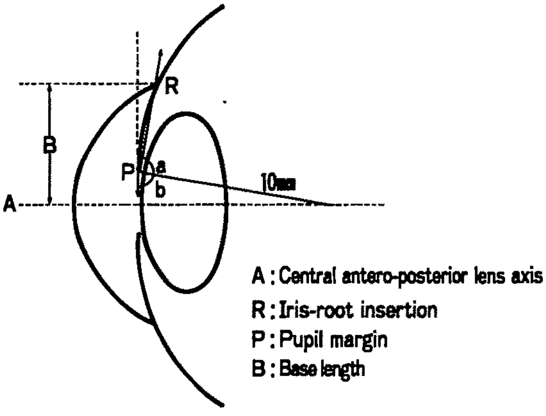

Fig. 5 *With a digitiser base length, pupil margin, iris-root insertion, central anteroposterior pupillary axis, angle a, and angle b are precisely estimated from the true image.*

From the true profile of the anterior chamber drawn by computer with a digitiser we can evaluate the direction of the vectors, such as pupil dilating force (D), iris-stretching force (E), and sphincter contracting force (S) as described by Mapstone.[10] The calculation of these vectors will result in the estimation of the value of the pupil blocking force (F) by the following equation:

$$F=(D+E)\cos a+S\cos b$$

where a is the angle consisting of both the vector (D+E) and the line from the pupil margin to the centre of the radius of the lens surface, and b is the angle consisting of both the vector S and the line from the pupil margin to the centre of the radius of the lens surface (Fig. 4). These angles (a,b) are estimated from the true image of the anterior chamber drawn by digitiser (Fig. 5). Thus we can calculate the pupil blocking force in each eye.

This new image analysis method of measuring the anterior chamber volume is convenient for both clinical examination and basic research. The precise evaluation of the anterior chamber volume provides beneficial data for physiopathological research into the dynamics of the aqueous humour, and the accurate profile of the anterior chamber provides important data for an analysis of the mechanism of glaucomatous attacks.

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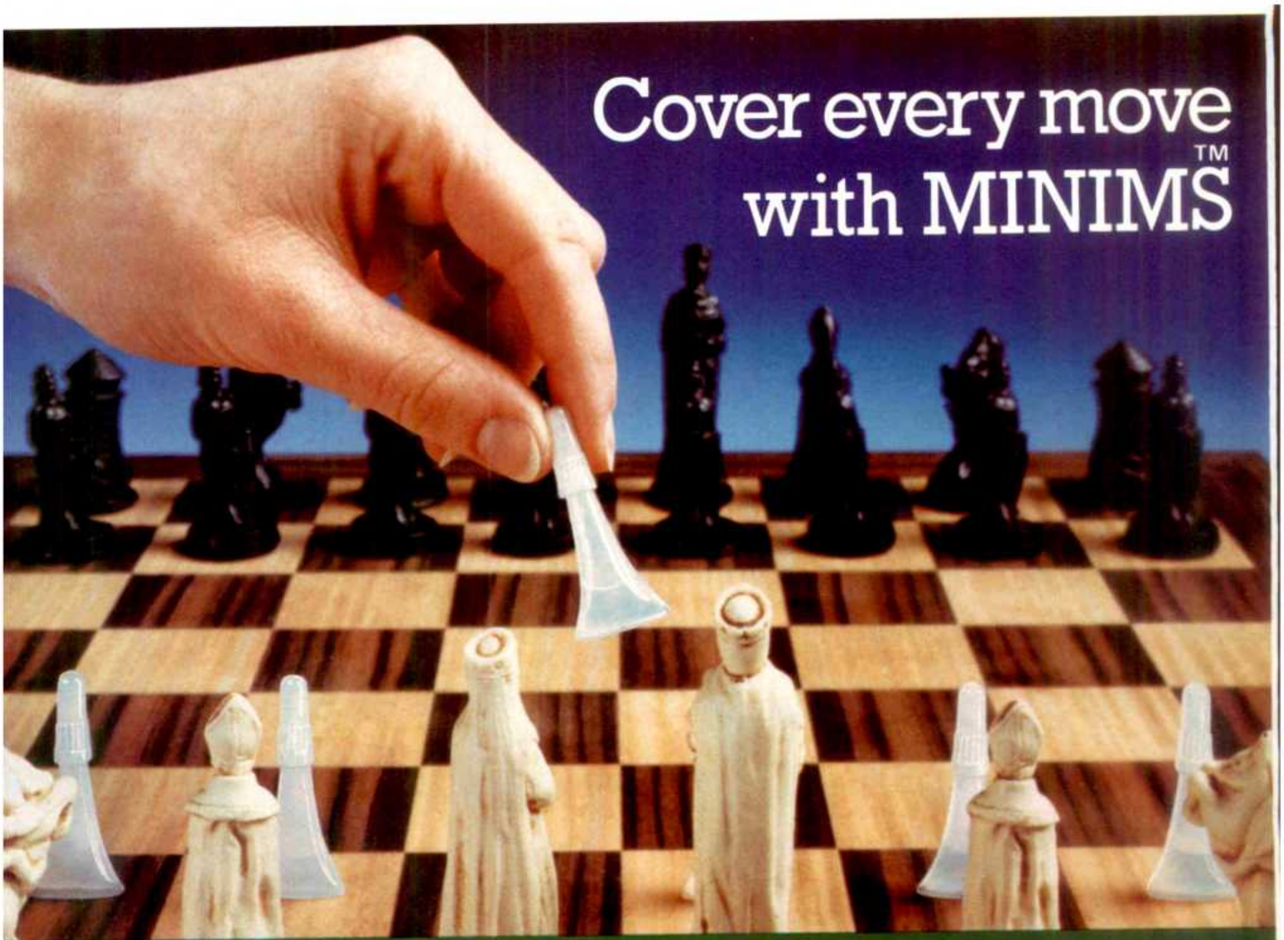

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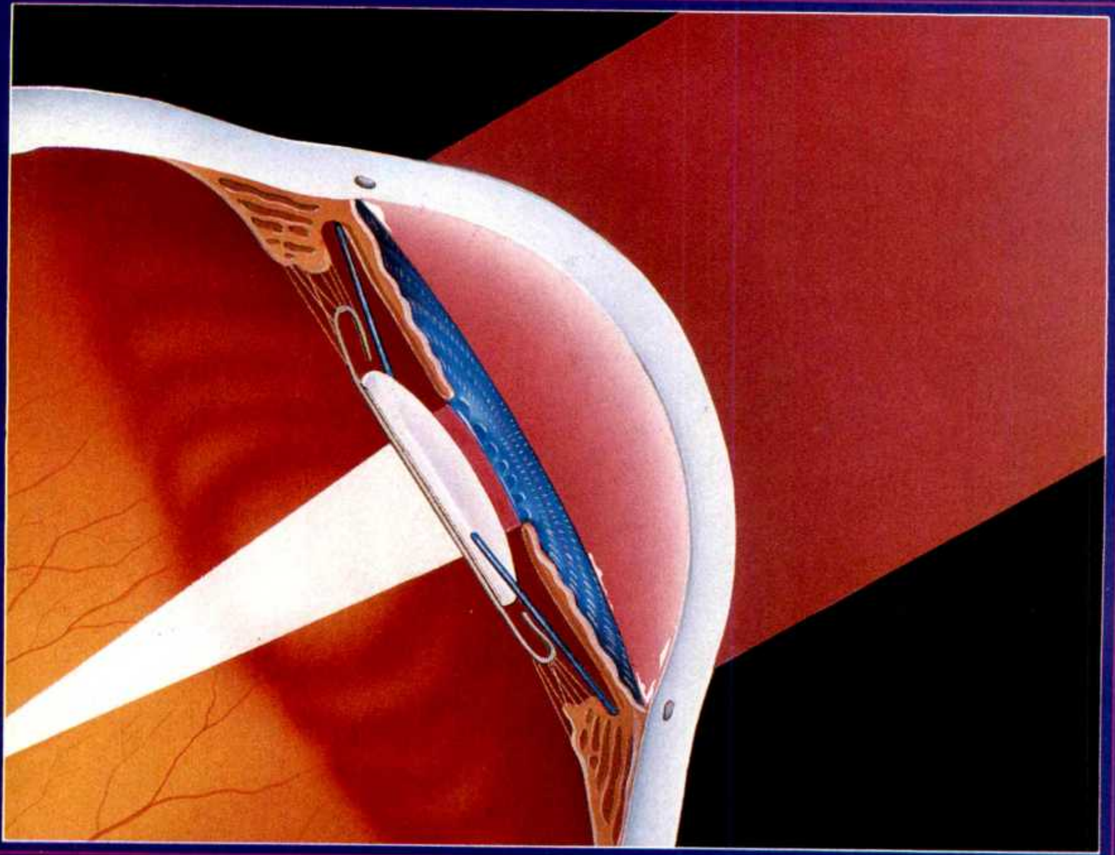

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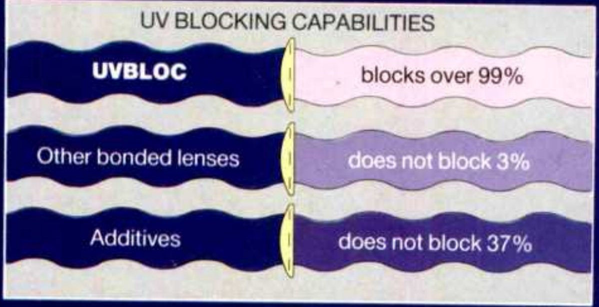

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Suppression and retinal correspondence in intermittent exotropia

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SUMMARY Suppression scotomas and retinal projection (retinal correspondence) were measured in six intermittent exotropes during deviation. Measurements used red-green anaglyph stimuli presented on a black background which could be varied from 3·4 minutes of arc to 3°24′. Results showed non-suppression of all points between the fovea and the diplopia point. Harmonious anomalous retinal correspondence was usually observed. Two subjects had spontaneous changes from anomalous retinal correspondence to normal retinal correspondence without a concurrent change in ocular position. Conventional testing resulted in more variable results in regard to retinal correspondence and suppression, suggesting that non-suppression and anomalous retinal correspondence occur when black backgrounds are used for testing.

Patients with intermittent exotropia of the divergence excess type (DE) or basic exotropia usually do not complain of diplopia when their eyes are deviating.[1] Parks[2] believes that the absence of diplopia is due to a dense temporal hemiretinal suppression. Using a technique employing Risley prisms, Jampolsky[3] demonstrated that DE patients have a suppression scotoma extending from the fovea to the point on the retina of the deviating eye which projects to the object of regard (point zero or diplopia point). Travers[4] and Pratt-Johnson and Wee[5] measured dense suppression scotomas at the fovea and point zero of the deviating eye in intermittent exotropes. Awaya *et al.*[6] measured suppression at the fovea and point zero in 11 of 25 of the intermittent exotropes that they tested, while using first degree target projected on a light fusional background.

The clinically accepted convention is that exotropes have a dense suppression in the deviating eye. There is, however, evidence suggesting that intermittent exotropes do not always suppress the deviating eye. First, DE patients can often experience diplopia when a red lens is placed over the fixating eye, while viewing a muscle light in a darkened room. Secondly, Cooper and Feldman[7] have demonstrated non-suppression of the fovea in the deviating eye of DE patients. Thirdly, DE patients often have non-suppression of the afterimage and anomalous retinal correspondence (ARC) in the deviated position and normal retinal correspondence (NRC) in the aligned position on the Hering-Bielschowsky afterimage test.[8]

We therefore attempted to qualify the depth of suppression in deviating intermittent exotropes while monitoring ocular position. We used variable first degree anaglyph targets to measure suppression scotomas. In the event of suppression we attempted to break the suppression and measure the retinal correspondence between point zero and the fovea of the deviating eye.

Subjects and methods

There were six subjects, four were female and two male. All had intermittent exotropia as measured by a distance and near cover test. Each was capable of performing in a restrained head apparatus and could give valid and reliable responses. They all had visual acuities correctable to at least 20/20 in each eye and could perceive at least 40 arc seconds of stereopsis on the Randot stereo test when binocularly aligned.

APPARATUS

An Atari 800 personal computer was used to present anaglyph stimuli on a Sony 19-inch (48-cm) Color Monitor.[9] The patient was seated 40 cm from the monitor and wore Keystone red-green glasses. The

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red lens was in front of the habitually fixating eye. The monitor displayed a red cross, which subtended an angle of 2°; each line of the cross had a width of 3·9 minutes of arc. The cross, viewed by the normally fixating eye, had a mean luminance of 2 cd/m². The second target was a green movable square or rectangle which also had a mean luminance of 2 cd/m². The green target could be instantly changed from a single-dot pixel (3·4 minutes of arc) to a 60-dot by 30-dot horizontal rectangle. The maximum green shape subtended an angle of (3°24′×1°42′) to the patient. The green target was movable so as to measure suppression areas. The background was black. The red and green targets were such that the red target could be seen only by the eye wearing the red filter and the green target by the eye wearing the green filter. Eye movements were monitored with a Biotronics Infrared Eye system combined with an auditory biofeedback apparatus. Thus the examiner was assured of stable deviation or alignment during testing. Ocular movements more than 1° from the present position (i.e., alignment or measured deviation position) resulted in an auditory tone (Fig. 1).

METHODS

The following conventional clinical tests were performed: Randot stereo test; troposcope evaluation of subjective and objective angles with a 1° target; Hering-Bielschowsky afterimage test; Bagolini striated lens test; and a red lens test for diplopia. All afterimage testing, Bagolini lens tests, and red lens tests were done in a darkened room. All ARC testing was done in both the aligned and deviated position.

Suppression areas and retinal correspondence were measured and recorded with the Atari 800 microcomputer and a colour TV monitor. The patient fixated the red cross while the examiner moved the green target. Initially the examiner determined the objective angle of deviation by means of occlusion (i.e., cover test). The green target was moved until no movement on the cover test was observed. The eye movement apparatus was then

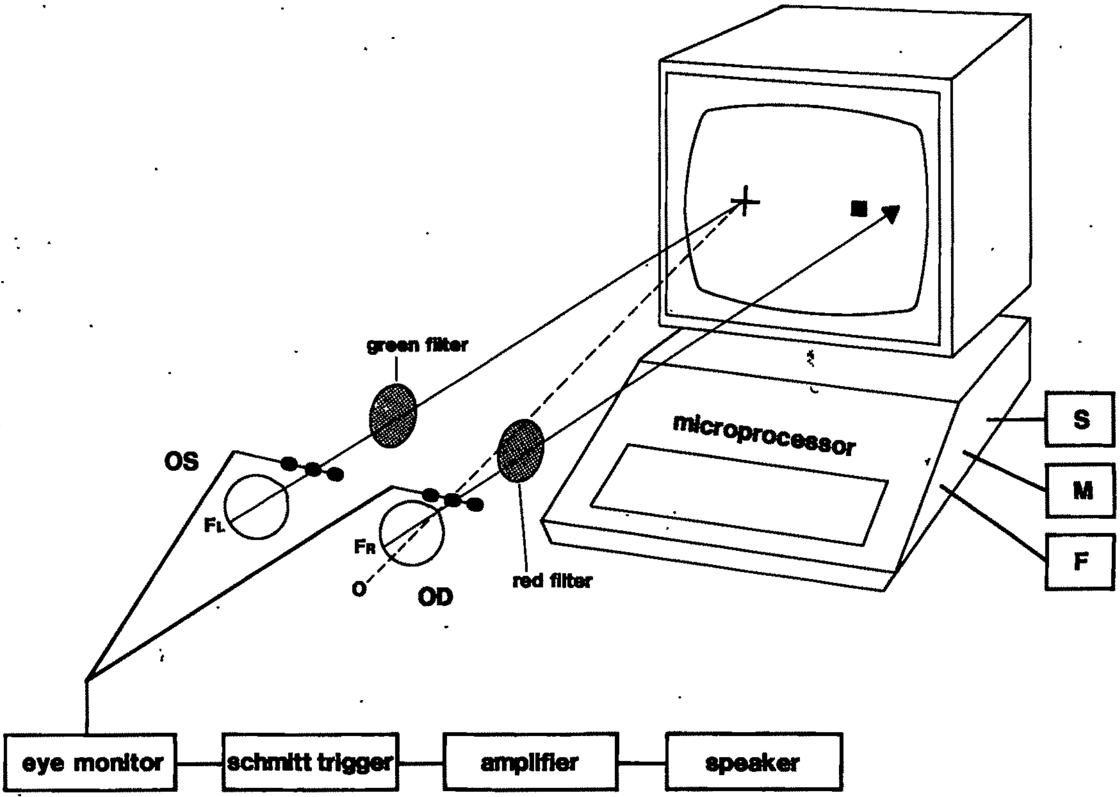

Fig. 1 *Patient is a right exotrope wearing red-green anaglyph glasses and infrared eye movement glasses. While viewing a colour monitor 40 cm away the patient fixates a red cross (+) with the OS and the examiner moves green box (■) seen by the OD. Examiner may control stimulus size with controller marked* S; *move stimulus with* M; *or move the fixation target with* F. $\mathrm{F_R}$ *is the fovea of the OD;* $\mathrm{F_L}$ *is the fovea of the* OS; *and* O *is point zero or the diplopia point. Ocular position during binocular perimetric evaluation is monitored with Biotronics eye movement monitor system.*

calibrated so that, when the left eye moved from its position, a tone was triggered, and when the right eye deviated a click was heard. The patient was then asked to describe the relative position of the red and green targets. He/she was also asked to report if either the red or green targets disappeared. The examiner then moved the green target until the patient reported superimposition (i.e., subjective angle).

The green target was moved through the visual field; the patient was asked to report any disappearance of either target. If the green target disappeared, the examiner used standard perimetric techniques to map out the scotoma. Larger targets were produced to determine the density of the suppression scotoma. Plots were done horizontally, vertically, and obliquely. Randomly placed points were also presented to pick up small scotomas and to verify kinetically determined retinal projection. Suppression areas were recorded by the examiner by depressing a button on the joystick controller.

Periodically during testing the patient was asked to point to either the fixation or the test target and to tell the examiner if either target ever disappeared. The patient was also asked to describe the relative position of each target. The examiner used 'catch trials' by extinguishing the stimulus to assure the validity of the patient responses.

Results

Table 1 presents both experimental and orthoptic findings in the six intermittent exotropes tested. Five of the six subjects showed no suppressions during experimental testing, even with the smallest possible target. The sixth patient suppressed all size targets throughout experimental testing. Four of the non-suppressing patients gave ARC responses, with one showing NRC. Two of the ARC responders (nos. 1 and 3) briefly changed from harmonious ARC to NRC without a concurrent change in ocular position during the course of testing. These two subjects usually showed ARC. One patient (no. 4) showed NRC responses throughout testing and had the largest deviation in the study on cover test.

Table 1 *Orthoptic and experimental findings*

PT	*DV CT*	*NV CT*	*TROP*	*EXP*	*BAG*	*HBD*	*HBA*	*RL*
1	30	20	Sup	NRC/ARC	ARC	ARC	NRC	Sup
2	20	14	Sup	HARC	ARC	NRC	NRC	Sup
3	45	50	Sup	NRC/ARC	Sup	NRC	NRC	Paradoxial dip
4	57	59	NRC	NRC	NRC	NRC	NRC	NRC
5	25	18	Sup	ARC	Sup	ARC	NRC	NRC
6	50	12	Sup	Sup	Sup	ARC	NRC	Sup

SUP=suppression. CT=prolonged cover test distance (DV) and near (NV) in prism dioptres to obtain maximum deviation. TROP=troposcope findings at the objective angle. EXP=red-green anaglyph findings during experimental testing. BAG=Bagolini lens results while an eye deviates. HBD=Hering-Bielschowsky test results during deviation. HBA=Hering-Bielschowsky test results during alignment. RL=red lens test results during deviation.

Standard clinical testing yielded more varied results. In the troposcope with first degree targets on a light background, five subjects suppressed completely and one showed NRC. Bagolini striated lens testing during deviation resulted in ARC responses for two subjects, NRC in one subject, and suppression for the remaining three subjects. The Hering-Bielschowsky afterimage test performed in a darkened room yielded three cases of ARC and three of NRC with no suppressions reported.

Discussion

Our results indicated the presence of non-suppression of luminous targets in five of the six patients across the temporal portion of the retina during experimental testing. ARC was found during deviation and NRC during alignment. These findings support Morgan's motoric theory of ARC.[10] However, neither Burian's[11] adaptation theory nor Morgan's theory are useful in explaining the instantaneous changes in correspondence without a concurrent change in ocular position observed in two patients in this study and in a previous study.[7]

The Hering-Bielschowsky and Bagolini lens tests which are used to determine the presence of NRC were done in a darkened room. The Hering-Bielschowsky test indirectly determines the presence of foveal suppression in either eye, while the Bagolini test indicates the presence of suppression at 'zero point'. It was shown that there was more suppression on the Bagolini test than on the Hering-Bielschowsky test, indicating that the zero point (diplopia point) of the deviating eye suppresses more readily than the fovea of the deviating eye. The clinical observation that it is more difficult to suppress the afterimages of the Hering-Bielschowsky test than the streaks of the Bagolini test in a darkened environment was confirmed by our study.

Our findings are consistent with Jampolsky's observation that not only size and brightness determine the extent of suppression. We found that colour complexity of the stimulus and similarity of targets presented to the two eyes may change suppression characteristics. Only one patient suppressed during our experimental procedure, which used different coloured stimuli on a black background. Pratt-Johnson and Wee[5] found both suppression of the fovea in the deviating eye and suppression of the deviating eye at the point matched to the fovea of the fixating eye (zero point). We believe that Travers's[4] use of non-illuminated targets and Pratt-Johnson and Wee's[5] use of a white background triggered suppressions and resulted in findings different from ours.

Awaya *et al.*[6] used a phase difference haploscope with and without a fusible background. Of the 11 intermittent exotropes tested, who had a manifest deviation during testing, nine showed suppression at point zero when a fusible background was present. Without a fusible background 15 showed suppression of the deviating fovea, and the remaining 10 showed superimposition at the objective angle. They concluded that intermittent exotropes have suppressions with NRC. We did not find the consistency of NRC nor the suppression that Awaya *et al.* reported.[6] These findings which differ from ours may be explained by the observation of Jampolsky[3] and Griffen[12] that differences in testing apparatus will alter suppression patterns.

Our findings suggest that the intermittent exotrope does not always suppress and usually has ARC under optimal conditions, even with very small stimuli. As previously stated, suppressions are dependent on the background. Black backgrounds seem to eliminate suppressions, while light backgrounds result in active inhibition or suppression. Our patients showed harmonious ARC, which extended from the point zero past the fovea and through the entire nasal retina. Like suppressions, the ARC is liable to change under certain test conditions. Retinal correspondence changes with ocular position and occasionally without any change in stimuli or eye movements.

These results may have important implications in the orthoptic treatment of intermittent exotropia. If techniques can be employed which disrupt both the anomalous retinal correspondence mechanism and the suppression mechanism, the DE patient will find it difficult to maintain deviation in the presence of NRC diplopia. Sanflippo and Clahane,[13] Cooper,[1] and Awaya *et al.*[6] have advocated diplopia awareness and antisuppression therapy in the treatment of intermittent exotropia. Our study suggests that one should start therapy with different coloured targets presented to each eye with a darkened background. Therapy continues by gradually increasing the ambient light and decreasing the filter intensity until the DE patient can experience NRC diplopia without the use of filters in a fully illuminated room. In this way one can be sure of breaking not only suppressions but ARC patterns as well.

In summary, our intermittent exotropes of the DE type did not show suppressions even with very small targets (3·4 minutes of arc.) at either the fovea or diplopia point of the deviating eye. Most of our patients showed harmonious ARC from the diplopia point to the fovea. Both suppression and retinal correspondence seem to change in accordance with stimuli, background, and retinal stimuli. Our results, which conflict with those of previous authors, are probably explained by accurate control of ocular position and use of a dark, non-fusible background with dissimilar targets. Our results suggest nonstability of a retinal correspondence (usually ARC) and non-suppression in the intermittent exotrope of the divergence excess type during deviation with small luminous targets on a dark background.

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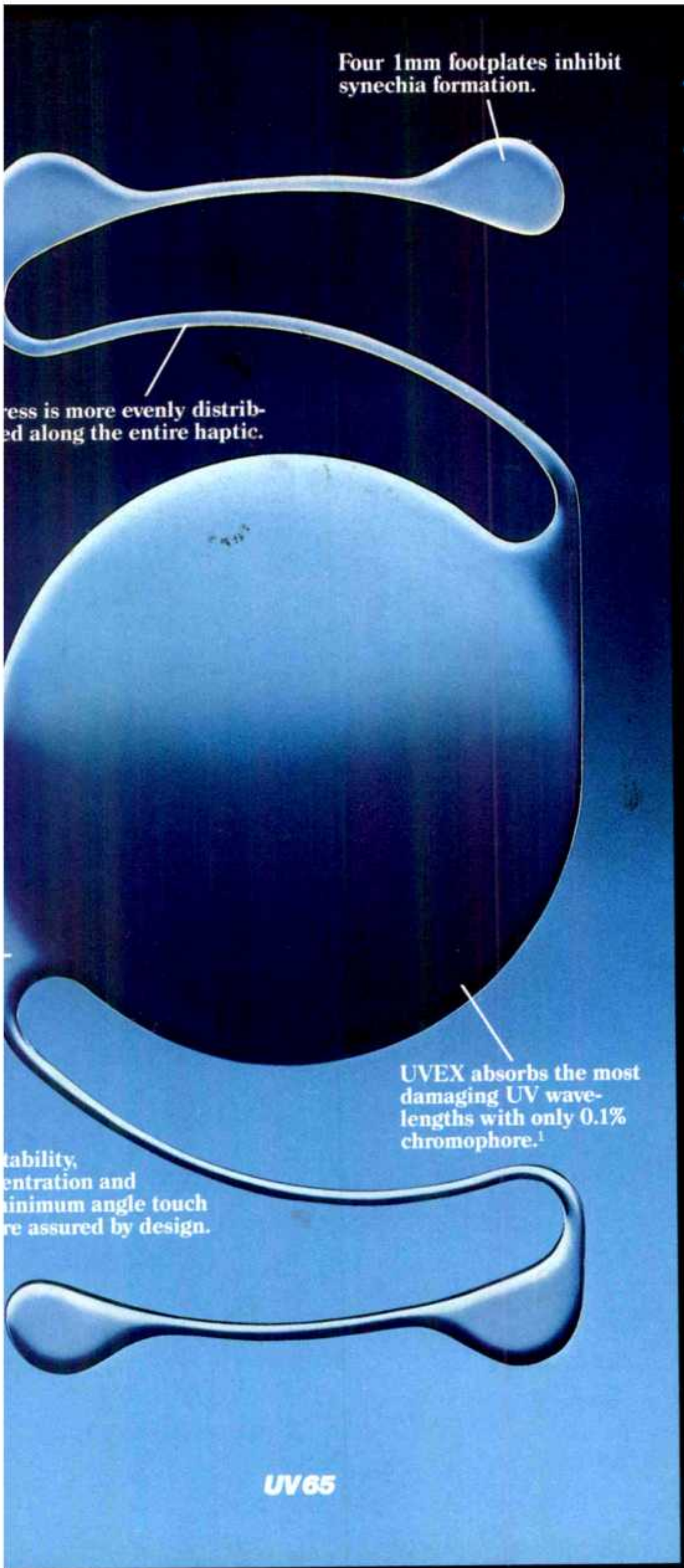
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Rapid diagnosis of *Chlamydia trachomatis* infection in patients attending an ophthalmic casualty department

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SUMMARY Direct immunofluorescence (DIF) techniques were compared with conventional cell culture for the diagnosis of ocular infections with *Chlamydia trachomatis*. The DIF test was found to have a sensitivity of 100% and a specificity of 97·5%. Of 178 patients studied, 19 patients (11%) were positive by DIF and 15 (8·4%) by conventional cell culture technique. Four patients who had previous treatment with chloramphenicol eye drops were negative by cell culture but positive by the DIF test. The DIF test is considered to be a rapid, accurate test with a number of advantages over culture techniques for the detection of *C. trachomatis*. The importance of appropriate referral of positive patients to prevent more serious sequelae due to *C. trachomatis* infection is discussed.

Much interest has recently been shown in the diagnosis of acute conjunctivitis, with emphasis on the importance of viral and chlamydial infections and the necessity to diagnose them accurately.[1-3]

One important cause of follicular conjunctivitis seen in an ophthalmic casualty department is infection by *Chlamydia trachomatis*. Other causes are associated with adenovirus and herpes simplex infections, and serious hospital outbreaks of adenovirus type 8 have occurred in the UK.[4 5]

C. trachomatis infections of the eye have been linked with genital tract infections.[3] As this organism is not eradicated by chloramphenicol, the usual broad spectrum antibiotic used in 'blind' therapy of bacterial eye infections, accurate differentiation between chlamydial and other bacterial infections is essential.[3-6]

It is now well recognised that genital infections due to *C. trachomatis* are increasing in the western world,[7] and it can be reasonably expected that a concomitant increase in *C. trachomatis* infections of the eye will occur. Genital infection due to *C. trachomatis* in women is often asymptomatic,[8] and the first indication of such infection may be conjunctivitis in the newborn. Infected infants will also carry *C. trachomatis* in the pharynx, and, if the eye infection is unrecognised and treatment withheld, pharyngeal infection may lead to severe pneumonia in the first few months of life.[9]

Until recently the only reliable method of identifying *C. trachomatis* infections was by isolation of the organisms in cell culture.[10] With the development of monoclonal antibody specific to *C. trachomatis* techniques have been devised for the identification of antigen directly in clinical specimens by means of fluorescein labelled antibody.[10-12]

This study compares isolation of oculogenital strains of *C. trachomatis* in cell culture with their direct identification in conjunctival smears.

Subjects and methods

One hundred and sixty-three patients (age range 13–55 years) presenting to the Casualty Department of the Bristol Eye Hospital with signs of acute follicular conjunctivitis between November 1984 and May 1985 were included in this study. Any patient who had clinical signs of bacterial conjunctivitis was excluded. In addition 12 neonates (10 days to 4 weeks) and three babies (10 weeks, 4 months, and one year) were also included.

A clinical history was taken and any previously used medication recorded. Patients were examined with a slit-lamp and any abnormality in the tarsal and bulbar conjunctivae, fornix, and lids noted. The cornea was examined and stained for signs of epithelial and subepithelial abnormalities or pannus formation.

Sterile cotton-wool swabs were applied vigorously to the lower lid conjunctivae of affected eyes to

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obtain a good yield of epithelial cells. Smears were prepared by rolling half the swab on to the centre of a 6 mm well of a Teflon-coated glass slide. The swab was then placed into sorbitol transport medium for isolation of chlamydia in cell culture. All specimens were placed at 4°C for up to four hours before being transported twice daily to the laboratory, where they were either immediately inoculated into cell cultures or snap frozen at −70°C.

Patients with suspected *C. trachomatis* infections were initially treated with tetracycline eye drops. All patients were asked to attend again approximately seven days later for re-examination and assessment of laboratory results. Where there was laboratory evidence of *C. trachomatis* infection, the diagnosis and implications were discussed with the patients before a two-week course of oral tetracycline was begun. Such patients were referred to the Department of Genito-Urinary Medicine at the Bristol Royal Infirmary for further investigation and contact tracing. Neonatal *C. trachomatis* infections were treated with both topical tetracycline eye drops and oral erythromycin and the parents referred for investigation and treatment.

LABORATORY METHODS

Chlamydia trachomatis isolation. Our standard methods of isolation in McCoy cell monolayers were used as previously described.[8] Briefly, specimens were inoculated on to coverslip monolayers of McCoy cells pretreated with cytochalasin B. After centrifugation at 3000 *g* for one hour at 34°C cultures were incubated for a further hour at 35·5°C before the inoculum and medium were removed and replaced with maintenance medium and reincubated for 68–72 hours. Cultures were washed in phosphate buffered saline (PBS), fixed in methanol, and stained with Giemsa. Stained coverslip monolayers were mounted and examined systematically by dark ground microscopy for typical intracytoplasmic inclusion bodies of *C. trachomatis*.

Direct immunofluorescence (DIF) of conjunctival smears. Smears were fixed in acetone for 5 minutes before being stained with a genus specific fluorescein isothyocyanate labelled chlamydia monoclonal antibody (Imagen Boots–Celltech) for 15 minutes.[10] Stained preparations were examined at a total magnification of ×1000. The whole of the stained smear was examined by the castle technique. Smears containing five or more cell-associated elementary bodies were considered positive.[10]

Table 1 *Comparison of direct monoclonal antibody immunofluorescence (DIF) with isolation of* C. trachomatis *in cell culture*

	DIF+	*DIF−*	*Total*
Culture +	15	0	15
Culture −	4	159	163
Total	19	159	178

Sensitivity 100·0%.
Specificity 97·5%.

Results

C. TRACHOMATIS ISOLATION IN CELL CULTURE

Of 178 patients with follicular conjunctivitis *C. trachomatis* was isolated from 15 (8·4%) in McCoy cell culture. These represented four males (18, 19, 22, and 23 years), three females (17, 18, and 20 years) and eight newborn babies.

IMMUNOFLUORESCENCE OF CONJUNCTIVAL SMEARS

On examination of the 178 conjunctival smears *C. trachomatis* antigen was detected in 19 by the direct monoclonal fluorescein labelled (DIF) reagent. Fifteen of these positive smears were confirmed by isolation of *C. trachomatis* in cell culture (see above). The four remaining smears (from 2 females and 2 neonates) were taken from patients who had received recent chloramphenicol treatment. Overall the examination of smears by the DIF technique had a sensitivity of 100% and a specificity of 97·5% (Table 1). Characteristically positive smears contained large numbers (>100) of brightly fluorescing, apple green, spherical elementary bodies. Occasionally cells contained intracellular antigen which resembled *C. trachomatis* inclusions in cell monolayers. These smears also contained copious amounts of a smaller particulate antigen similar to that observed previously in urogenital specimens and were present only in smears containing >1000 elementary bodies.[10]

The adult patients with follicular conjunctivitis in whom *C. trachomatis* was identified all presented with sore, red, watery eyes of between five days' and three weeks' duration. Six were monocularly affected and three were affected binocularly. On examination, in addition to the follicular conjunctivitis, two had superficial punctate keratitis and one mild pannus formation.

The 10 newborn babies in whom *C. trachomatis* was identified all presented with sore, red, sticky eyes at between 10 days and 11 weeks old. The symptoms started four to 14 days post partum; six were unilaterally and four bilaterally infected.

Discussion

Previous studies have shown that *C. trachomatis* infections of the urogenital tract can be diagnosed rapidly by examination of clinical specimens by *C. trachomatis* genus specific[10] or species specific[11–12] monoclonal antibodies in a direct immunofluorscent (DIF) system. We have extended the application of this technique to the diagnosis of *C. trachomatis* in patients presenting with follicular conjunctivitis and have shown that the diagnosis can be made from conjunctival smears in under one hour from receipt of the sample in the laboratory.

At the time of this study using the genus reactive monoclonal antibody, 10 or more elementary bodies in a smear were recommended by the manufacturer as being diagnostic of a *C. trachomatis* infection. We consider that, provided sufficient experience has been gained, diagnosis of *C. trachomatis* infections can be made when five or six cell associated elementary bodies are present in a smear.[10] Although we used this criterion, low levels of elementary bodies were never detected in this study. Positive smears containing more than 1000 elementary bodies often contained large numbers of brightly fluorescing particulate bodies, which probably represent the glycolipid, genus reactive, heat stable antigen.[10] At present further studies are in progress to clarify this observation.

A particular advantage that direct immunofluorescence has over conventional isolation of the organism in cell culture is the ability to detect chlamydia antigens in patients who have had inappropriate antibiotic treatment such as chloramphenicol. It is recognised that chloramphenicol is unreliable in resolving *C. trachomatis* in vivo but does interfere with the replication of *C. trachomatis* in vitro.[6] Perhaps it is the number of viable elementary bodies in the eye which is the limiting factor in determining whether *C. trachomatis* may be isolated in cell culture following treatment with chloramphenicol. In our study four of 19 patients with *C. trachomatis* infections had had previous chloramphenicol treatment and the organism was not isolated in cell culture. These infections would not have been diagnosed without the introduction of the DIF test. Following laboratory diagnosis of *C. trachomatis* infection in these four patients appropriate antimicrobial therapy was instigated, with rapid resolution of the clinical symptoms. In contrast *C. trachomatis* was isolated in cell culture from one patient following chloramphenicol treatment. A further important aspect of the laboratory diagnosis of *C. trachomatis* is in those instances where herpes simplex virus infections may be diagnosed clinically without laboratory verification. Under such circumstances patients have been treated empirically with 5-iodo-2-deoxyuridine (IUDR), which is recognised as enhancing the replication of *C. trachomatis* in vitro. In vivo the severity of *C. trachomatis* infection has been shown to be increased after treatment with IUDR.[13]

In a previous study in Bristol *C. trachomatis* was isolated from 13 (3%) out of 449 patients studied.[3] In that study neonatal *C. trachomatis* infections were not considered. Apart from our neonatal study group *C. trachomatis* was identified in 9 (5·5%) out of a total of 163 adult patients tested.

The laboratory confirmed diagnosis of *C. trachomatis* in our adult population occurred in the age range 17–23 years, which is in agreement with previous observations[3] and confirms that these infections occur in young, sexually active, often single adults. The importance of this diagnosis indicates the need for referral to a urogenital clinic for further investigations and appropriate treatment of their partners to avoid more serious sequelae in females such as acute salpingitis[14 15] or infertility.[16 17]

Similarly the identification of neonatal *C. trachomatis* conjunctivits may be the first indication of an asymptomatic cervical infection in the mother, which also requires further investigation as outlined above. Furthermore prompt diagnosis is essential in newborn babies to enable the appropriate antimicrobial therapy (oral erythromycin and topical tetracycline) to be instigated to prevent those rare cases of lower respiratory tract involvement[18 19] which have been reported in the UK. Neonatal infections are acquired at birth and conjunctivitis may appear five to 14 days later.[20] This incubation period is a useful indicator and allows differentiation from other bacterial infections. In rare cases chlamydia conjunctivitis appears earlier than five days if the membranes rupture shortly before term.[20]

Before the development of the DIF test for detecting antigen directly in clinical samples, serology was also used as a presumptive indicator of a current *C. trachomatis* infection of the eye.[2] We consider that direct antigen detection in smears prepared from infected conjunctiva has advantages over serological tecniques and has an associated higher degree of specificity. Furthermore this technique gives a more rapid result and does not suffer from the drawbacks of storage, transport, and contamination which are associated with a culture based service.[10]

We appreciate assistance from Professor D L Easty, and the co-operation of the staff of the Bristol Eye Hospital Casualty Department.

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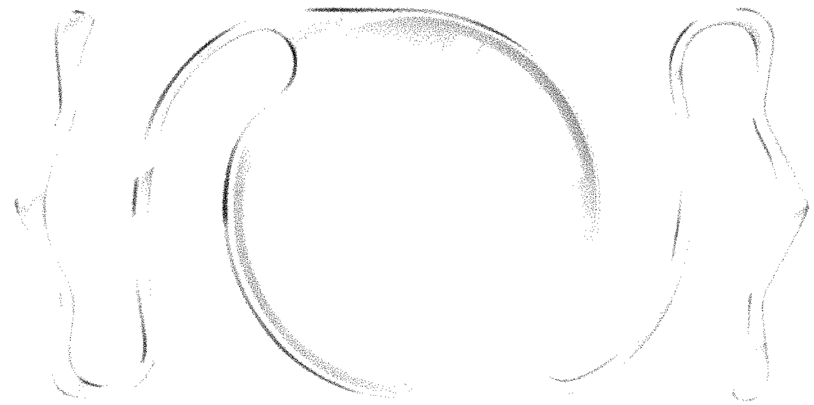

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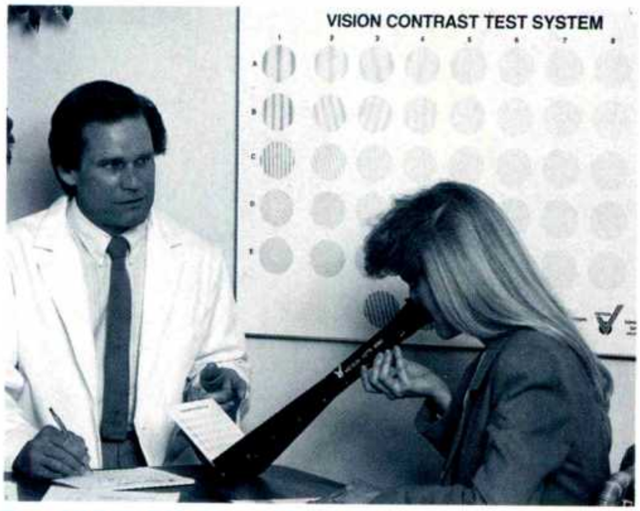

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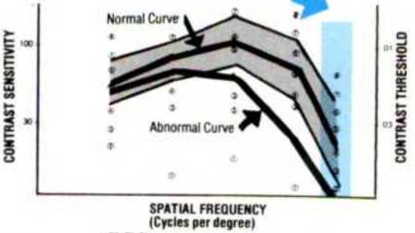

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British Journal of Ophthalmology, 1986, **70**, 681–685

Lacrimal sac mucoepidermoid carcinoma

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SUMMARY A single case of mucoepidermoid carcinoma of the lacrimal sac was considered worth reporting as there are only four other cases described in the literature. The importance of the correct histological diagnosis and the management are discussed. This appears to be the first study of the ultrastructure of lacrimal sac mucoepidermoid tumour.

Mucoepidermoid carcinoma is a tumour composed of neoplastic mucin-producing cells and epidermoid cells. Although it most frequently affects the salivary glands it has also been reported in the ophthalmological literature in the conjunctiva[1-3], lacrimal gland,[4], and lacrimal sac[2,5].

Case history

A 78-year-old woman was seen in December 1979 for examination of a swelling in the region of the left lacrimal sac which had been present for some months. Her corrected visual acuity was right eye 2/60, left eye 6/6. Uncomplicated intracapsular cataract extraction had been performed on the right eye in 1977, but the central vision had remained poor owing to maculopathy attributed to injury some years before.

A firm, solid, painless mass was palpable in the left lacrimal fossa. There was no proptosis and no discharge on pressure on the sac. X-rays of the orbits and paranasal sinuses revealed one large ethmoid cell on the left side with smooth margins, but tomography of maxillary[5] and orbital areas revealed no evidence of bone destruction. At surgery the mass was found to be adherent to skin and firmly fixed to underlying periosteum. When removed it measured 14×8×6 mm.

Pathological examination showed a mass of fibrous tissue in which lay scattered numerous islands of squamous cells (Fig. 1) in different configurations.

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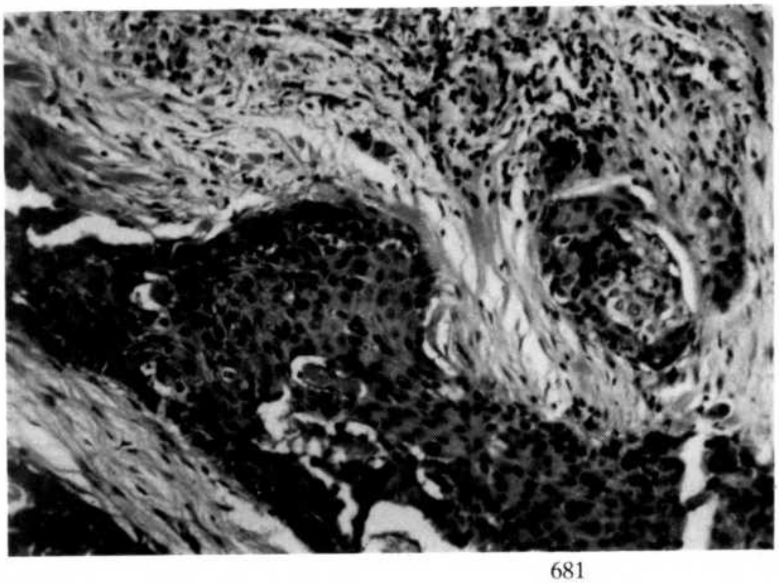

Fig. 1 *Squamous cell clumps.* (H & E, ×32).

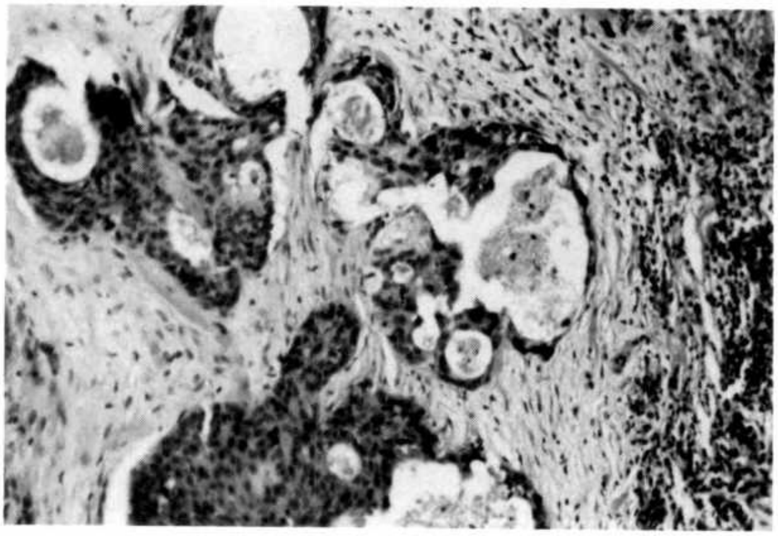

Fig. 2 *Squamous cells and microcystic area.* (H & E, ×32).

There were foci of microcystoid (Fig. 2) areas which stained positively for mucin, and many scattered clear cells could be seen. Bundles of voluntary muscle were scattered throughout, with evidence of muscle invasion as well as some degree of secondary myositis. In focal epithelial aggregations the cells could be described as being transitional in type. There was a moderate amount of mitotic activity. The histological diagnosis was that of a typical mucoepidermoid carcinoma.

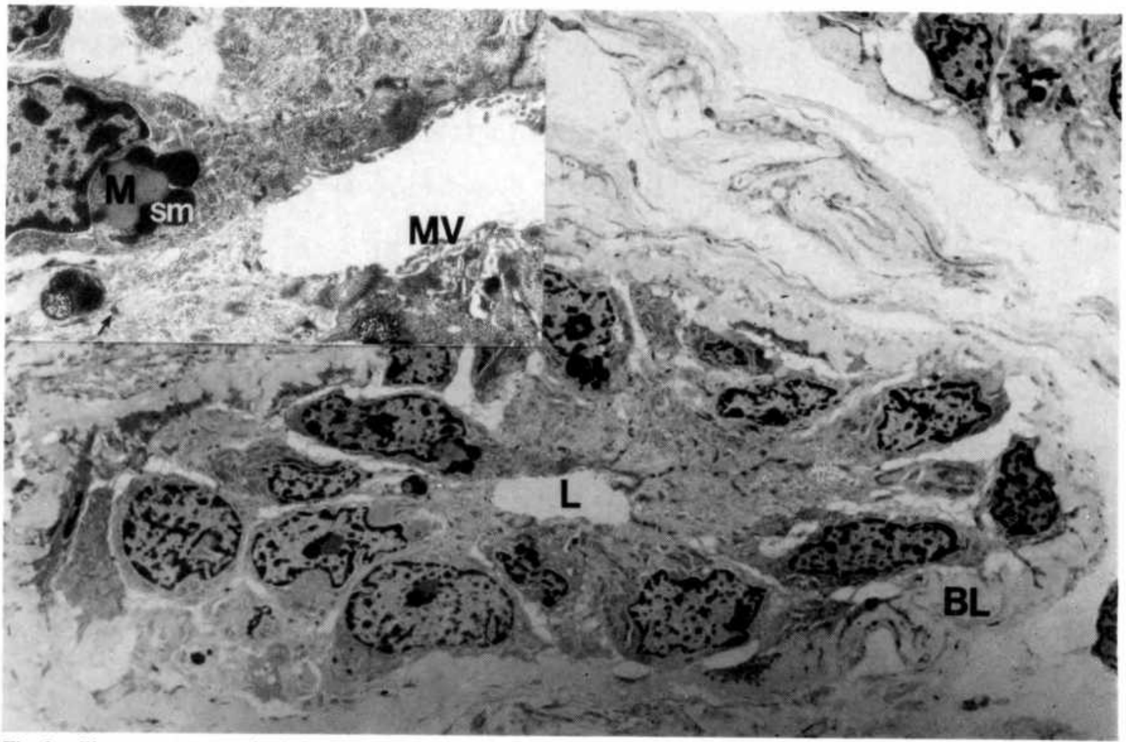

Fig. 3 *Electron micrograph. Columnar and polygonal shaped cells, bound by a basal lamina* (BL) *and forming a lumen* (L). *The luminal surfaces bear microvilli* (MV) *and desmosomes are identifiable. Mucin* (M) *and seromucin* (SM) *vacuoles are present in some of the cells (insert). (×2600, inset ×9400).*

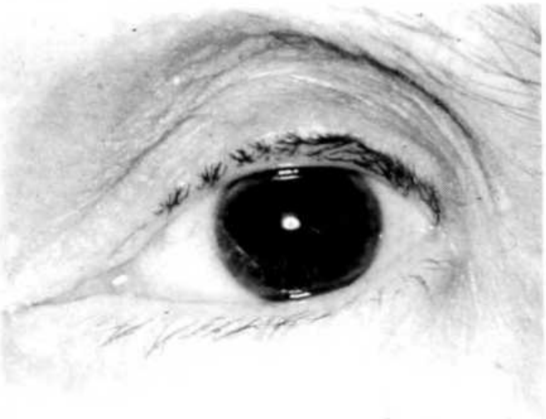

Fig. 4 *Appearance after first operation—slight epiphora.*

Tumour tissue in 1 mm cubes was removed from the paraffin embedded specimen and processed for electron microscopy. The tumour cells, which were polygonal, elongated, and columnar, were surrounded by a basal lamina, to which they appeared attached. Both mucous cells and intermediate cells were found in close association with occasional lumen formation (Fig. 3). The mucus-secreting cells contained membrane bound mucin, filled vacuoles, and occasional seromucinous secretory vacuoles. Some cells also contained endoplasmic reticulum. Mitochondria, fine filaments, and glycogen granules were either absent or inconspicuous. Desmosomes and tonofilaments were easily identified. The luminal surface of both the mucus-secreting and the intermediate cells were characterised by microvilli.

Examination by a specialist physician revealed no sign of metastatic spread and an ear, nose, and throat examination revealed no abnormality (Eric Fenelon, FRCSI). Thereafter she remained symptom-free (Fig. 4) for 3½ years apart from a brief period of slight epiphora.

In December 1983 the patient attended again with a firm mass which displaced the eye upwards and forwards and was disposed in crescentric manner from the inner half of the left upper eyelid, around the inner canthus and into the medial two-thirds of the lower eyelid.

Ultrasonography showed two deposits on the medial side of the orbit, the more anterior of which was situated 6 mm behind the anterior corneal plane. Computerised tomography scan (Fig. 5) (after intravenous contrast) disclosed an infiltrating, enhancing, soft tissue mass along the medial margin of the left orbit, extending laterally to the globe and anteriorly also towards the medial canthus, the bulk of the tumour being located in the medial interior part of the orbit. There was no evidence of bone destruction. A biopsy showed a similar appearance to the original specimen, the squamous cells being morphologically very prominent. Mucin was also identified.

At subsequent operation (Fig. 6), in March 1984, as much of the tumour as could be removed without damage to the eye was excised. Microscopic examination of this most recent specimen showed mucoepidermoid tumour with considerable dedifferentiation and with hyperchromatism and mitotic activity. Normal lacrimal sac mucosa was identified, with tumour in the deeper layers, and there was extensive infiltration of muscle.

In December 1984, five years after the patient first presented, she retained a visual acuity of 6/9 in the left eye, though that had now become immobile and showed lagophthalmos and early signs of exposure keratitis. She declined further surgery on grounds of age and general frailty.

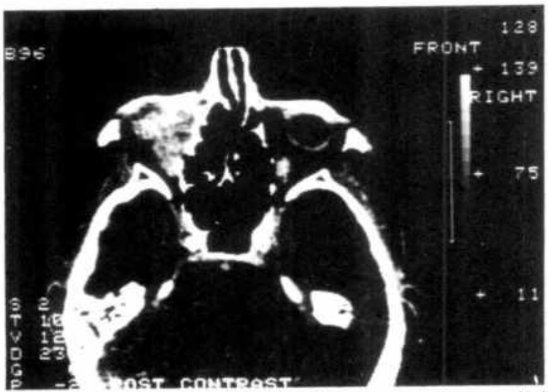

Fig. 5 *Infiltrating, enhancing, soft tissue mass along medial margin of orbit.*

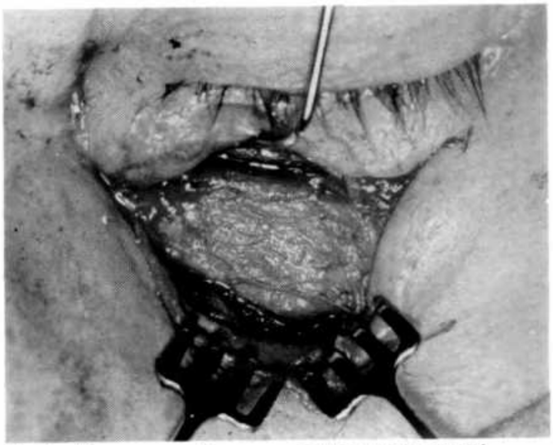

Fig. 6 *Recurrence of tumour—early stage in surgical exposure.*

Table 1 *Summary of reported cases of lacrimal sac mucoepidermoid carcinoma*

Authors	*Age, Sex, Race*	*Mass*	*Pain*	*Discharge*			*Duration of symptoms (years)*	*Proptosis*	*Extra-ocular muscle restriction*	*Bone destruction on X-ray*	*Size of mass in mm*	*Exenteration*	*Follow-up or present status*
				Watery	*Purulent*	*Bloody*							
Bambirra *et al.*[5]	58 M Brazilian	+	+	+	–	–	2	+	+	–	10×8 (max. diam.)	+	Well 2 years later
Ni *et al.*[2]	60 M Chinese	+	–	–	–	–	3	–	–	+	20×20 ×15	+	Died 1 year later of cardiovascular disease. No recurrence
Ni *et al.*[2]	40 F Chinese	+	–	+	+	+	2	+	+	+	30×25 ×25	+	No recurrence after 17 years
Ni *et al.*[2]	19 F Chinese	+	–	–	+	–	1	–	–	+	30×30 ×15	+	No recurrence after 5 years
Blake *et al.*, this paper	78 F Irish	+	–	–	–	–	¼	+	+	–	14×8 ×6	–	Well 5 years later, but eye fixed, exposure keratitis

Discussion

The occurence of this tumour in other sites is well defined in both the pathological and general surgical literature. Seven cases have been reported in the conjunctiva[1 3 4]. Harry and Ashton[7] reviewed lacrimal sac tumours in the files in the Department of Pathology at the Institute of Ophthalmology in London over a 20-year period (1948–1967). Thirteen cases were found, eight being epithelial in origin, and they concluded that all of these were of transitional cell type. They proposed a classification of: type 1 (transitional cell papilloma); type 2 (intermediate transitional cell tumour); and type 3 (transitional cell carcinoma). Squamous metaplasia was a feature of many of the growths, but mucoepidermoid tumours per se were not described. So far as can be ascertained, there are only four reports of mucoepidermoid tumours arising in the lacrimal sac, the first case being described in Brazil in 1981 by Bambirra *et al.*[5] Three more were reported by Ni *et al.* (1983) from Shanghai.[2] Table 1 summarises these reports and includes the present case.

Ni *et al.*[2] postulate that mucoepidermoid carcinoma in the lacrimal sac area may arise from either lacrimal sac mural serous gland epithelium or from the columnar epithelium of the conjunctiva with its goblet cells. These tumours may infiltrate locally and rarely metastasise; only in very few cases does invasiveness assume serious proportions.[8] All patients reported upon with mucoepidermoid carcinoma underwent exenteration, and the early invasion of near-by voluntary muscle would tend to confirm that this may be the required procedure. This option was not readily open to us, since from the standpoint of visual acuity we were dealing with an only eye. The advanced age of the patient also argued in favour of a conservative approach, which in the event allowed her five years of good vision. Prognosis, now that further surgery has been declined, is poor: vision will be lost through exposure keratitis and optic atrophy.

A diagnosis of squamous cell carcinoma was made in a general pathology laboratory which received the specimen from the present patient before it was referred to this centre, when the mucoid element was identified. We believe that more of these growths may on further investigation and examination be found to be of mucoepidermoid type, but could have been missed because of the rarity of reports of such neoplasms at this site.

We thank Mr R Lester and Miss M Hurley for technical help, Mr S Travers for photographic assistance, and Miss C Tyner for secretarial work.

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Immunogenetic studies in retinoblastoma

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SUMMARY In three unrelated families with transmitted retinoblastoma 43 members were tested for HLA-A, B, C, and DR antigens. On 18 patients, 16 unaffected relatives, and 16 controls, mixed lymphocyte cultures were carried out and the response to mitogens, phytohaemagglutinin, concanavalin A, and pokeweed mitogen examined. There were no associations of retinoblastoma with any HLA antigen. A reduction in T cell function is suggested by the results of the mitogen tests.

Retinoblastoma, with an incidence in North-east England of 1 in 16 000, is a malignancy that poses many problems. In some patients it can develop almost at birth and pursue a relentless course despite vigorous and sophisticated treatment, while in other members of the same family the disease, although presumably caused by the same gene, behaves very differently. One member of the first family in the present investigation (II, 12) had a large tumour necessitating enucleation at 6 weeks of age, but a similar tumour in the other eye underwent spontaneous regression. Her sister (II, 14) had one eye completely free of tumour but had a large regressed tumour in the other. A third member (II, 4) had small flat calcified lesions in both eyes, while in the preceding generation the father of these three patients was found at necropsy at the age of 73 to have a dormant, apparently viable, 'retinoma.' Retinoblastoma can present at any age, though usually in infancy; it may affect one or both eyes; it may occur and then spontaneously regress; there may be endophytic, exophytic, or diffuse infiltrating growth; if untreated it is likely to cause death, usually within two years but possibly as late as eleven years from onset, or in a minority of cases an early tumour may regress. There are inherited and non-inherited forms.

To account for the considerable intrafamilial variability that occurs clinically, and the occurrence of occasional spontaneous regression, it has been suggested that retinoblastoma may have some immunogenetic basis. It is possible that, besides an inherited tendency to maldevelopment of a group of retinal cells, there is also some immunological mechanism which controls tumour proliferation, with some variation in the efficiency of the host immune response to specific tumour antigens. Thus bilateral retinoblastoma would develop where the response is absent, or is too inefficient to control a developing tumour. In some cases of unilateral retinoblastoma the immune response triggered by the initial development would be sufficiently powerful to inhibit tumour development of cells in the other eye. Spontaneous regression would occur when a tumour starts to develop, initiates a highly successful response, is inhibited by it at a critical stage, and then retrogresses. There would thus be an underlying continuum to what appear to be discrete categories of bilateral tumours, unilateral tumours, spontaneous regression, and unaffected carriers. The present study was undertaken to explore this hypothesis further.

Three immunogenetic studies of HLA types in retinoblastoma have been reported. In a group of 122 patients Bertrams *et al.*[1] found a decreased frequency of HLA-B12 and an increased frequency of HLA-Bw35, the latter being significant only among hereditary cases. Segregation analysis of 64 families did not show any significant deviations from expected values. Gallie *et al.*[2] did not find any significant associations with HLA-A or B antigens in 102 cases. They did, however, observe increased Dw2 and decreased Dw1 frequencies in patients with regressed

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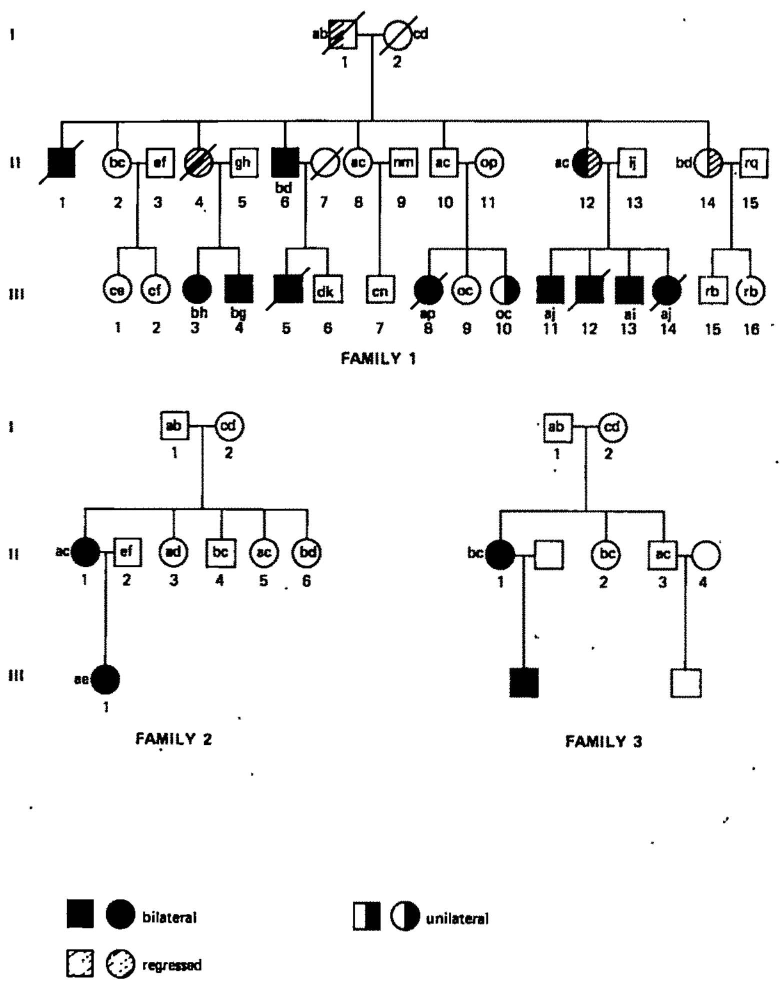

Fig. 1 *The three families and the HLA types.*

Key to Haplotypes (the gene combination on each chromosome):

Family 1

a: A2, Bw44, DR7
b: A3, B7, DR2
c: Aw23, Bw51, DR5
d: Aw24, B5, DR1
e: A9, B12, Cw1, DR4
f: A9, B27, Cw2, DR5
g: A2, B7, DR2
h: A3, B7, DR3
i: A2, B12, DR1
j: A3, B18, DR3
k: Aw30, B7, DRw6
m: A1, B14, DR blank
n: A2, Bw44, DR4
o: A2, B8, DR5
p: A2, Bw44, DR7
q: A2, B7, Cw2, DR2
r: A2, B27, Cw3, DR4

Family 2

a: A1, B8, DR7
b: A1, B8, DR3
c: A2, B7, DR5
d: A3, B40, Cw3, DR4
e: A2, B18, DR1
f: A2, B18, DR3

Family 3

a: B14, DR1
b: A2, Bw44, DR2
c: A11, B27, DR1
d: A1, B15, Cw3, DR4

compared with non-regressed tumours. A study[3] of some members of the first of the families reported on here showed no evidence of association between particular HLA haplotypes and retinoblastoma, but suggested decreased responsiveness in mixed lymphocyte cultures of patients by comparison with those in whom spontaneous tumour regression had occurred.

The present study concerns three families in the Newcastle upon Tyne region with transmitted retinoblastoma. The pedigrees are shown in Fig. 1. Their members were typed for HLA-A, B, C, and DR antigens, and one-way mixed lymphocyte cultures (MLC) were set up between members within each family. The mixed lymphocyte reaction is considered to be an in vitro correlate of in vivo graft rejection. In addition cell mediated immunity was investigated in vitro by measuring the lymphocyte transformation in response to stimulation by a standard pool of allogeneic cells and by three mitogens–PHA (phytohaemagglutinin), con A (concanavalin A), and PWM (pokeweed mitogen). PHA and con A are T cell mitogens, whereas PWM stimulates proliferation of both T and B cells. No patient had received any recent drug therapy likely to affect the results. Controls were healthy unrelated age matched individuals tested in parallel with the families.

Materials and methods

Cell separation. Mononuclear cells were separated from whole blood by density gradient centrifugation, washed, counted, and stored in liquid nitrogen until required. Purified B cells required by HLA-DR typing were obtained following a two-step density gradient centrifugation procedure, in which T cells were separated by E rosetting with sheep red blood cells, and monocytes were removed by an initial incubation with carbonyl iron. B cells were stored at 4°C for three or more hours prior to DR typing.

HLA typing. Samples were tested against a panel of highly purified HLA antisera by a standard two-step microlymphocytotoxicity test, with at least two antisera per antigen.

Mixed lymphocyte cultures. For each test 50 000 responding cells and 50 000 mitomycin-C treated stimulating cells were cultured together in 150 μl culture medium for 120 hours at 37°C in a humidified atmosphere of 95% air and 5% carbon dioxide. At 97 hours cultures were pulsed with 1 μCi tritiated thymidine; at the end of the culture period cells were harvested, and incorporated thymidine was determined by liquid scintillation counting. For each individual an unstimulated culture of responding cells and culture medium alone, and a standard culture of responding cells and standard pooled stimulating cells, were included. All cultures were performed in triplicate. The results were expressed as median counts per minute (cpm) corrected for background by subtraction of the median cpm of the unstimulated culture. Relative response values were calculated by dividing the corrected response by the corrected response to standard pooled cell stimulation (%RR).

Mitogen test. 50 000 responding cells were cultured with suboptimal, optimal, and supraoptimal concentrations of each of three mitogens, PHA, and con A (90 hours' incubation), and PWM (114 hours' incubation). Incorporation of thymidine was determined as for the MLC test. The results were expressed as median cpm for each triplicate culture corrected for background by subtraction of the median cpm of unstimulated cultures.

Table 1 *Pooled cell stimulation*

	n	*Mean±SEM*	
Controls	29	22 927±1581	
Unaffected family	18	18 313±1366	$p<0{\cdot}05$
Patients	11	16 077± 878	$p<0{\cdot}02$

Results

HLA TYPING

The distribution of HLA haplotypes in each family is shown in Fig. 1. For family 1 the typing results were in agreement with those given by Jones.[3] There was no evidence of crossovers within the HLA region in any of the families. There was no evidence of association of retinoblastoma with any HLA antigen. Both of the patients with regressed tumours possessed DR2, but so did four of the 10 affected.

MIXED LYMPHOCYTE CULTURES

Table 1 gives the corrected response to standard pooled cells in three groups: patients, unaffected family, and unrelated controls. The mean responses in the patient and family groups were significantly lower than for the control group ($p<0{\cdot}02$ and $p<0{\cdot}05$

Table 2 *MLR between individuals with one DR antigen in common*

Responders	*Stimulators*	*n*	*%RR (mean±SEM)*
Unrelated			
Controls	Controls*	10	80·3±4·2
Unaffected family	Controls†	16	58·7±5·8
Controls	Unaffected family‡	17	60·4±3·8
Patients	Controls*	16	52·1±4·7
Controls	Patients	12	61·7±7·5
Related			
Unaffected family	Patients	16	40·4±3·5
Patients	Unaffected family	18	38·8±4·2
Unaffected family	Unaffected family	37	39·9±2·8
Patients	Patients	13	33·4±3·7

*$p<0{\cdot}001$. † $p<0{\cdot}02$. ‡ $p<0{\cdot}01$.

Table 3 *MLR between individuals with no DR antigen in common*

Responders	*Stimulators*	*n*	*%RR (mean±SEM)*
Unrelated			
Controls	Controls	20	87·7±4·1
Unaffected family	Controls	28	88·5±5·4
Controls	Unaffected family	29	85·7±3·7
Patients	Controls	27	79·1±5·2
Controls	Patients	21	77·5±7·4
Related			
Unaffected family	Patients	18	64·1±4·9
Patients	Unaffected family	22	60·4±4·6
Unaffected family	Unaffected family	14	70·4±5·2
Patients	Patients	27	59·7±3·7

No significant differences between groups.

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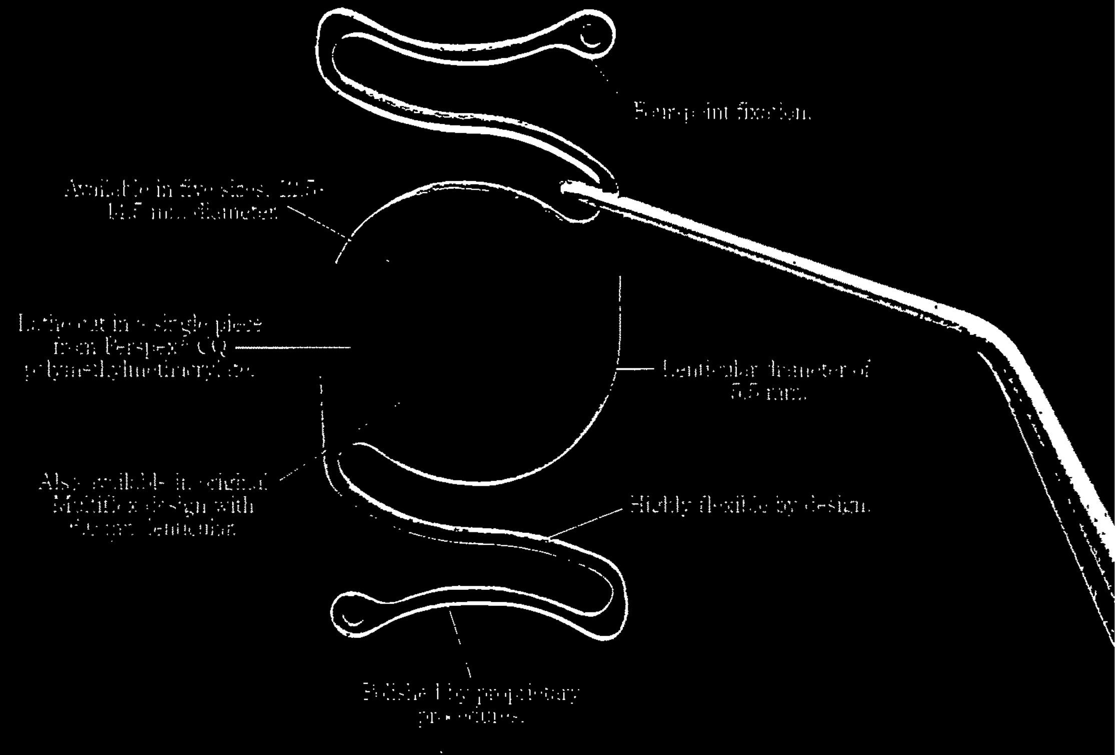
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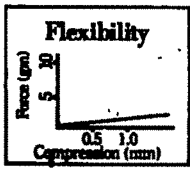

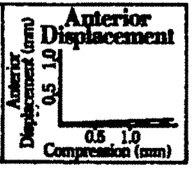

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respectively). The two patients in whom a tumour had regressed lay towards the lower end of the distribution of patient responses. Relative responses in mixed lymphocyte cultures were then grouped according to disparity at the HLA-DR locus; mean relative responses among patients, family members, and controls are given in Table 2 (one DR antigen shared) and Table 3 (no DR antigens shared). There were no significant differences between groups in the mixed lymphocyte reaction between related individuals. Among unrelated individuals there were no significant differences between groups not sharing any DR antigens. In unrelated groups sharing one DR antigen the mean response in the controls versus controls group was significantly greater than in family versus controls ($p<0\cdot02$), controls versus family ($p<0\cdot01$), and patients versus controls ($p<0\cdot001$).

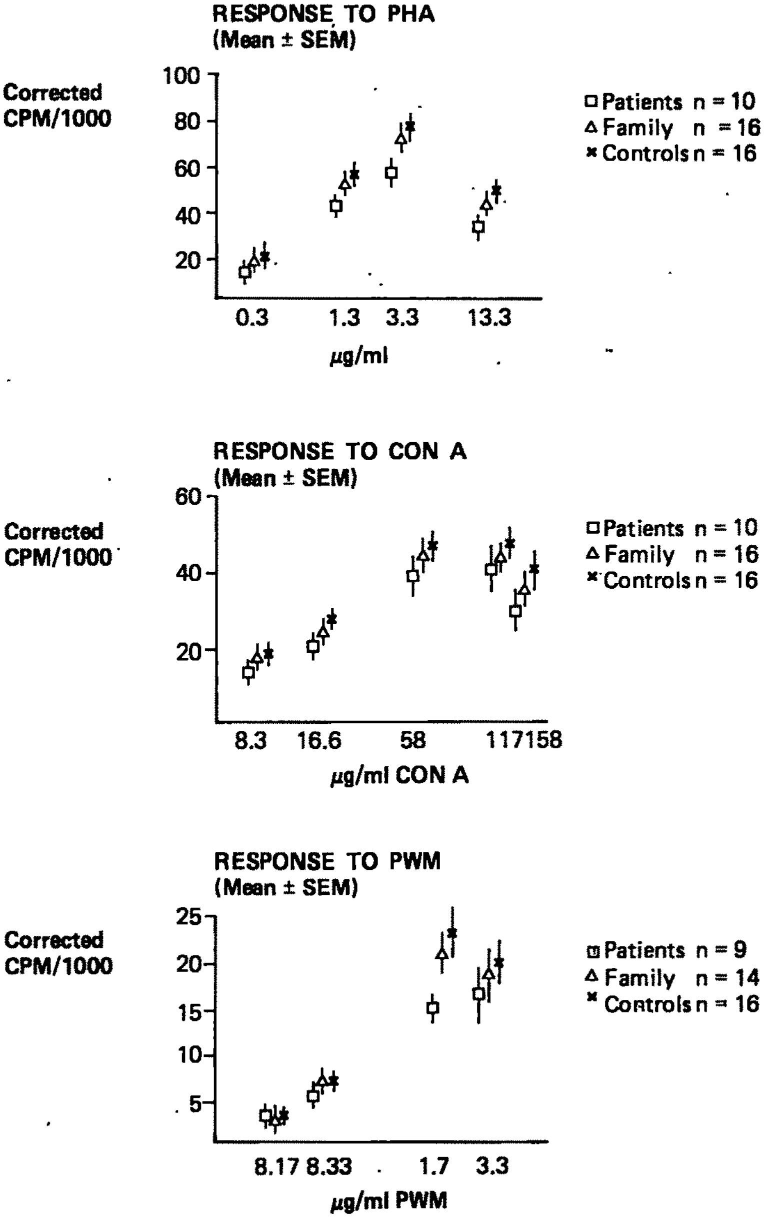

Fig. 2 *Mitogen responses.*

MITOGEN TESTS

The mean responses to each mitogen in the patient, unaffected family, and control groups are shown in Fig 2. No significant differences were observed between unaffected family and control groups. However, patients responded less well than controls to mitogen stimulation: they differed significantly in PHA ($p<0·02$ at 1·3 μg/ml and $p<0·05$ at 3·3 μg/ml), in optimal PWM stimulation ($p<0·05$ at 1·7 μg/ml), and in suboptimal con A stimulation ($p<0·05$ at 16·7 μg/ml). Again, the two with regressed tumours were at the lower end of the distribution of responses. The only significant difference between patient and family groups was for PHA at 1·3 μg/ml ($p<0·05$). Multiple linear regression analysis also revealed a significant difference for PHA stimulation between family and patient groups ($p<0·05$), and between control and patient groups ($p<0·01$).

Discussion

The possibility of involvement of immunogenetic mechanisms in the development and regression of retinoblastoma has been discussed on several occasions—for example, by Gallie *et al.*[4] and Roberts and Aherne.[5] The present results give some support for this.

While HLA typing of the subjects did not reveal any significant non-random segregation within families, and as expected there was no evidence of linkage or association with retinoblastoma, the lymphocyte transformation tests, which measure the afferent arm of the immune response, and the results of the mixed lymphocyte reaction, are more positive.

The three mitogens used here stimulate different but overlapping lymphocyte populations. PHA mainly stimulates proliferation of the majority of T cell subpopulations; con A is also a T cell mitogen, which activates different subpopulations at different doses—helper cells at suboptimal doses, and most T cell populations at optimal dose. PWM stimulates both T cells and B cells. In mixed lymphocyte cultures the response to a standard pool of stimulating cells is a measure of the ability to respond, by T helper cell proliferation, to allogeneic challenge.

The results indicate that in vitro lymphocyte transformation in response to these non-specific mitogens is reduced among retinoblastoma patients compared with controls. Mean responses among unaffected family were intermediate between the patient and control groups. Moreover the reduced MLR to allogeneic cells not only confirms but goes further than the results of the earlier study of family 1,[3] for it takes into account the fact that the extent of the reaction reflects the degree of histocompatibility between the individuals tested, and especially at the HLA D/DR locus. Hence MLC comparisons need to be made within groups of subjects with similar degrees of disparity—that is, having two haplotypes in common, one haplotype, or no haplotype in common. In the present study significant differences occurred in the one haplotype disparate group, where the mean response in patients versus controls, unaffected family versus controls, and controls versus unaffected family was below that in controls versus controls. The responses to the mitogens and allogeneic cells in combination suggest a general depression in cell mediated immunity, and particularly a reduced T cell function in patients.

No studies of general cell mediated immunity in retinoblastoma have been reported, most immunological studies focusing on the reactivity of patients to tumour cell lines and the characterisation of immune complexes,[4 6-8] and as yet the antigens in such reactions are poorly characterised. However, a reduction in cell mediated immunity has frequently been observed in patients with other malignant disease, such as chronic lymphocytic leukaemia, Hodgkin's disease, and carcinoma of the breast, lung, and colon.[9-11] There are conflicting opinions on whether this degree of depression correlates with disease activity.[12-14] Initially it was assumed that the reduced cell mediated immunity resulted from an impairment of the cell populations directly involved in the responses being measured. Today, however, there is increasing evidence that these cell populations are functionally intact but are actively inhibited by the action of suppressor cell populations, particularly suppressor T cells and monocytes, for their removal often restores in vitro proliferative capacity to normal levels in most patients.

The reduction in in-vitro lymphocyte proliferation in retinoblastoma patients in the present study might be mediated by active suppressor mechanisms as described in other malignancies.[15-18] However, alternative explanations must also be considered. There might be a reduction in the number of circulating T cells, or an alteration in the ratio of T cell subsets, or there could be a specific defect in the proliferative capacity of the responding T cell populations. There is no evidence of a specific impairment in the ability to recognise cell surface antigens.

In the mitogen and MLC tests the lower level of response in the two with regressed tumours may be partly a function of their older age. However, Berlinger and Good[19] studied cancer free individuals from family aggregates of hereditary colonic carcinoma and found that in individuals with no evidence of precancerous disease the response to allogeneic stimuli was decreased. This deficiency could in some cases be attributed to the suppressive influence of adherent cells (monocytes) on normally responding lymphocytes. A similar pattern was observed in the present retinoblastoma families. Unaffected family members showed a significantly reduced response to allogeneic cells but did not differ in mitogen responsiveness. This group was heterogeneous, since it included both those without retinoblastoma and the silent transmitters, and it would be worth inquiring whether the reduced cell mediated immunity is restricted to the latter.

Acknowledgment is gratefully made to Dr A W Craft for assistance with the families, and to the Cancer Campaign for Research (North of England Council) for financial support.

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Role of sphincterotomy in extracapsular cataract surgery

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SUMMARY Forty patients subjected to extracapsular cataract extraction with posterior chamber intraocular lens implantation in whom a sphincterotomy was required are reported on. This method was used to counter the problems created by a small pupil during surgery. The technique is described and results evaluated.

Extracapsular cataract surgery with posterior chamber intraocular lens implantation has gained widespread popularity over the last 10 years. However, there is reluctance to perform this procedure in eyes known to have poor dilatation of the pupil because of the potential for increased surgical problems. We describe techniques using a peripheral iridectomy extended to form a sphincterotomy, designed to overcome the technical difficulties. We evaluate the results of 40 operations and review the literature.

Material and methods

We tried to dilate the pupils preoperatively with 2 drops of phenylephrine 10% and 4 drops of cyclopentolate 1% at 10-minute intervals starting one hour before surgery. Eleven patients received general and 29 local anaesthesia. The latter consisted of a retrobulbar injection of a mixture of 2 ml 2% lignocaine and 2 ml 0·5% bupivacaine with 1/200 000 adrenaline in which was dissolved 1500 IU hyaluronidase, followed by 10 minutes of gentle manual bulbar compression. A Pierse wire speculum was inserted. A superior rectus fixation was used only when exposure of the superior limbus was inadequate. A reverse slope corneal section down to Descemet's membrane was made from 10 to 2 o'clock at the apex of the limbal arcade of vessels with a diamond knife, skirting anterior to any drainage bleb present.

As will be seen, the procedure used varied at this point. In the main group of patients (B, below) a puncture was made in the section at 12 o'clock, large enough for the entry of a Steriseal cystotome which was attached to a bottle of balanced salt solution (BSS) and used to make an inferior half beer-can anterior capsulotomy. The wound was opened and a small peripheral iridectomy was performed at 12 o'clock. Sphincterotomy was achieved with straight Vannaş scissors through the apex of the iridectomy. The sphincterotomy pillars could be swept aside or incarcerated in the wound to allow good exposure of the superior half of the anterior capsule. Healon (Na hyaluronate) was used during this manoeuvre when required to maintain a deep anterior chamber. The superior half of the capsulotomy was then completed, ensuring an opening of adequate size. The nucleus was expressed with an irrigating vectis, and soft lens matter aspirated, the anterior chamber depth being maintained by irrigation from a bottle of BSS via a Steriseal straight coaxial cannula. We aimed to clear all the posterior cortex and leave a clean posterior capsule. Air and/or hyaluronidase was then instilled, the Rayner Y loop offset lens inserted and dialled 90°, and the wound was closed with four or five interrupted 10/0 nylon (Ethicon) sutures.

The patients reviewed fell into three groups (Table 1):

Group A. The capsulotomy was carried out through a small pupil, and sphincterotomy was

Table 1 *Surgical procedure*

	No. of eyes	*Technical success*	*IOL implanted*	*Complications*
Group A	11	8	7	2 Completed 1 Vitreous loss
Group B	19	18	17	1 Vitreous loss
Group C	10	10	10	—

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carried out after a difficulty was encountered during expression of the nucleus.

Group B. In patients whose pupils were rigid and undilatable because of synechiae or miotic effects the sphincterotomy was carried out before completion of the capsulotomy.

Group C. A final group underwent division of the sphincter because the pupil came down during the manipulation of the cataract, usually during aspiration of cortex.

Results

Forty of 495 consecutive patients submitted to extracapsular cataract extraction for posterior chamber intraocular lens implantation underwent sphincterotomy (Fig. 1).

Group A (11 eyes). In two eyes the lens was expressed completely, leaving no posterior capsule, and in one eye vitreous followed the nucleus by herniation through a tear in the posterior capsule. The method was successful in seven eyes, though one required a second procedure to implant the lens because it had been wrongly thought that the posterior capsule had been breached at the time of extraction. One eye was not implanted because the anterior chamber depth could not be maintained. This eye subsequently required further aspiration of residual lens cortex. All these operations were technically difficult and the method was abandoned.

Group B (19 eyes). No difficulties were encountered during capsulotomy and nucleus expression, though one eye lost vitreous through a tear in the posterior capsule during aspiration of the cortex, and one eye was not implanted because of difficulty in maintaining the anterior chamber depth. One eye in this group presenting with a contusion cataract had a dense anterior capsular plaque which could not be pierced with a cystotome, and the anterior capsulectomy was carried out with microscissors after sphincterotomy to improve exposure. In two patients the sphincterotomy was performed first, after opening of the wound, and the capsulotomy was carried out under hyaluronate.

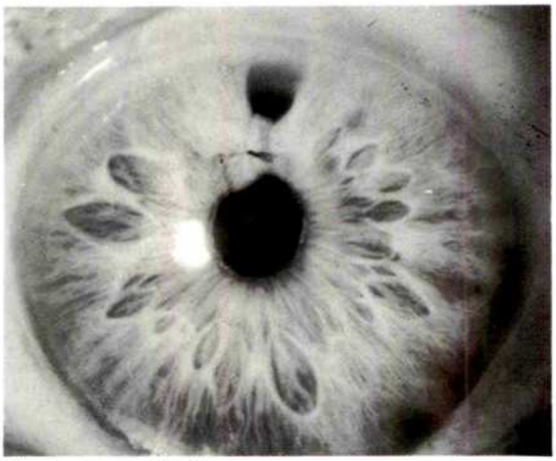

Fig. 1 *A sutured sphincterotomy.*

Group C (10 eyes). All these operations were technically successful. See Table 1.

Except for eyes which were not implanted 22 sphincterotomies were closed by a single 10/0 nylon tie and 12 were left open. Four eyes of the unsutured group and two of the sutured group produced adhesions between the iris pillars and the free edge of the remaining anterior lens capsule. Such adhesions were usually seen in association with displacement of the intraocular lens. Only one eye, with an unsutured sphincterotomy, developed a localised sector of entrapment without persistent inflammation soon after surgery; 22 months later this had not progressed. Three eyes with resutured sphincters developed updrawn pupils because of misplaced iris sutures. This exposed a dialling hole in one, as did leaving the sphincter unsutured in two others. Two of the three patients affected experienced a ghost image to one side, but neither was concerned by this.

POSTOPERATIVE COMPLICATIONS

Glaucoma. Patients without preoperative glaucoma had no significant postoperative ocular hypertension. Among the 17 patients who had glaucoma before the operation, postoperative control, defined as intraocular pressures less than 22 mmHg on the same or less medication as before operation, was as good or better in 12 patients and worse in two apart from those not implanted. Both patients whose control worsened had angle closure glaucoma requiring topical medication preoperatively, and both had undergone previous peripheral iridectomy.

Uveitis. A fibrinous exudative uveitis was often seen during the first 48 hours after operation. This settled rapidly on topical steroid drops in all but three

Table 2 *Visual outcome*

Acuity	*Group A*	*Group B*	*Group C*
6-5–6/9	6	9	8
6/12–6-/18	3*	5*§‖	2*¶
<6/18	2†‡	5† (3‡**)	

Additional pathology:
*Senile macular degeneration.
†Disciform maculopathy.
‡Advanced glaucoma.
§Amblyopia.
‖Congenital nystagmus.
¶Branch retinal vein occlusion.
**Corneal scarring.

eyes, which had postoperative uveitis for longer than six weeks. One case, lasting three months, had a past history of uveitis. One case of uveitis lasted six months without obvious cause, and one patient still has uveitis after 10 weeks, associated with residual lens cortex in the pupillary area.

During follow-up of 1.5–22 months no instance of retinal detachment, endophthalmitis, cystoid macular oedema, or corneal decompensation has occurred. The visual outcome is presented in Table 2, together with reasons for unsatisfactory results.

Discussion

Broad iridectomy is a time honoured aid to extracapsular surgery in eyes where the pupil cannot be dilated.[1] We present our experience of a group of patients with this problem in whom we wished to implant a posterior chamber intraocular lens. Unlike broad iridectomy, our technique involves the excision of a small peripheral iridectomy alone, with no loss of iris sphincter as has been advocated previously,[2] and our results show it to be a safe method.

A small pupil may be encountered for a number of reasons (Table 3). Most commonly it is due to synechiae from past glaucoma surgery or uveitis. Though greater dilatation may be achieved by release of synechiae at surgery allowing preoperative mydriasis to take effect, this is often insufficient and usually short lived because of the iris irritation inevitable in their breakdown. Hyaluronate can be used to widen a pupil mechanically during capsulotomy, but the mydriasis may not be maintained once the section is opened. Long-standing miotic therapy is another major factor in poor preoperative dilatation. Altering the regimen to avoid miotics for several weeks prior to surgery may help, but patients on long term pilocarpine are likely to have sphincter hypertrophy and even posterior synechiae, and they may remain unresponsive to mydriasis. Seventeen of 40 (42·5%) patients with glaucoma submitted to intraocular lens implantation required a sphincterotomy. Patients noted to have exfoliation of the lens capsule, even without raised intraocular pressure or glaucoma, often required a sphincterotomy. Diabetics also required a sphincterotomy more frequently than others, for five of 11 (45·5%) such patients underwent the procedure.

Table 3 *Cause of poor dilatation*

Posterior synaechiae	
Previous peripheral iridectomy (1 diabetic)	8
Previous drainage surgery	1
Past uveitis	4
Argyll Robertson pupil	1
Open angle glaucoma: long-term therapy (1 diabetic)	8
Pseudoexfoliation syndrome (1 diabetic)	5
Diabetic iridopathy	1
Poorly maintained mydriasis (1 diabetic, 1 uveitis, 2 insufficient drops)	11

Patients with glaucoma or a past history of uveitis presented only minor additional technical difficulty, though some of the glaucoma patients required prolonged aspiration of copious cortex and often developed a marked fibrinous reaction for the first two postoperative days which responded readily to topical steroid treatment.

Induction and maintenance of a dilated pupil is usually achieved by a combination of sympathomimetic and anticholinergic agents. Recent studies have shown that miosis induced by surgery is due to a number of factors, including trigeminal nerve stimulation, prostaglandin release from the iris, and release of substance P from sensory nerve endings within the eye.[3] Both topical and systemic prostaglandin inhibitors as well as topical local anaesthetics administered before surgery have been advocated in order to help maintain pupil dilatation.[4-6] Substance P inhibitors may have a role in the future.[3]

Maintenance of a dilated pupil during surgery can be helped by minimising manipulation of the iris and by intracameral administration of dilute epinephrine as a direct injection or in the irrigating solution.[7,8] Use of viscous intracameral solutions may also help, as may peroperative injection of subconjunctival Mydricaine Formula 2 (atropine sulphate 1 mg, procaine HU 6 mg, adrenaline solution 0·12 ml).

Despite these pharmacological and mechanical manoeuvres to induce continued mydriasis, there are a number of eyes in which the problem remains. Surgeons using phacoemulsification may still be able to complete their extraction through a semidilated pupil, but even this technique is difficult through pupil less than 4 mm in diameter. Praeger improves visualisation by using an angled iris retractor,[2] but with a nuclear cataract he advocates a small sector iridotomy. Peterson found a small sphincterotomy to achieve a 4 mm pupil before phacoemulsification useful, and advised against a full sphincterotomy for fear of iris pillar synechiae and subsequent pupil entrapment.[2] Hoffer has found it possible to perform a formal extracapsular extraction by gently massaging the nucleus through a miotic pupil, which then remains fixed at 6–7 mm because of the multiple sphincter ruptures produced,[2] but we found this hazardous. Welch has performed small sphincterotomies at 12, 4.30, and 7.30 o'clock positions prior to capsulotomy. He has also proposed a trapdoor capsulotomy which is swept through the wound and secured to the sclera to retract the superior iris.[2]

However, this may risk extension of the capsular tear into the zonule with subsequent vitreous loss. Kokoris has used a collar button iris retractor with infusion during the anterior capsulotomy and maintains the anterior chamber with hyaluronidase.[2] Simcoe has advocated expression of the nucleus in eyes with small pupils by the use of a small loop made from a 1-inch (2·5-cm) 25-gauge blunted needle placed on a tuberculin syringe. Removal of cortex is then facilitated by retracting iris, either with forceps or a blunt hook, temporarily encarcerating the iris in the wound, or by using retraction sutures.[9]

We began by making a sphincterotomy after the capsulotomy in eyes in which a small pupil had made expression of the nucleus difficult, but experienced an unacceptable complication rate. Therefore we consider early sphincterotomy preferable to provide an adequate capsulotomy fashioned under direct vision. Vectis expression then becomes straightforward and tears in the remaining capsule unlikely. Aspiration of cortex is greatly helped by the increased exposure provided. This is especially important in that eyes requiring sphincterotomy often undergo prolonged aspiration for removal of tenacious cortex.

The sphincterotomy may be sutured after insertion of the intraocular lens. This is cosmetically satisfactory, allows near normal iris function, and keeps the iris taut in front of the lens plane, reducing the risk of posterior synechiae and subsequent pupil entrapment. However, our results were similar in both the sutured and unsutured groups. Only one eye with an open sphincterotomy developed synechiae between the pupil margin and the capsule. Even this did not progress to form entrapment after 22 months of follow-up. The risk of entrapment can be minimised by repositioning the iris pillars in front of the intraocular lens after dialling is complete, for iris pillar synechiae did not cause problems, and no progression was seen. More recently sphincterotomy has been used purely to facilitate aspiration of cortex when the pupil constricts excessively during surgery. Complications often arise under these circumstances because the aspiration becomes a blind procedure. Improved visualisation reduces the risk of surgical problems, and our results have been technically successful in all eyes so treated.

CONCLUSION

Sphincterotomy is a safe aid to extracapsular cataract surgery, providing increased exposure during critical manoeuvres within the eye. It allows for an adequate anterior capsulotomy, enabling easier nucleus expression and complete aspiration of lens cortex. Posterior chamber intraocular lenses can be inserted safely, and they remain stable with or without closure of the sphincter. The procedure may also be employed to facilitate aspiration of lens cortex should the pupil constrict during operation.

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The burden of genetically determined eye disease

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SUMMARY We determined the underlying aetiology of blindness for the registered blind population of the Province of Newfoundland and Labrador. In both 1981 and 1984 single-gene disorders accounted for 30% of total blindness and congenital defects for another 10–11%. Genetically determined conditions, diabetes, and senile macular degeneration (SMD) were the three leading causes of registration in each year, 1980–4. We calculated mean ages of registration and mean ages of death over the last four years for five major aetiological groups. Patients with genetic conditions were registered at a much younger age and had a correspondingly longer duration of blindness (21 years as compared with 5 years for either diabetes or SMD). Total 'person-years of blindness' was then calculated from the product of this duration of blindness and the total numbers registered in each group. This index shows that the overall individual and population impact of monogenic blindness is overwhelmingly greater than that of other causes (6849 person-years compared with 270 for diabetes and 430 for SMD). In view of this frequency and duration of monogenic blindness, and also of the substantial hereditary liability to relatively common causes of blindness such as glaucoma, diabetic retinopathy, and high myopia, we suggest that more attention needs to be paid to elucidating the genetic contribution to blindness.

There is a growing awareness of the importance of genetic disease as a cause of blindness. For example, a recent paper from Saudi Arabia[1] reported a changing pattern of aetiology, so that fully 84% of childhood blindness in that country is now caused by hereditary conditions.

Three years ago we reported on the causes of registered blindness in Newfoundland at the end of 1981.[2] Our aim was to determine as accurately as possible the underlying aetiology of blindness in each case, based on a review of the files of all persons registered with the Canadian National Institute of the Blind (CNIB) and examination of as many as possible of those cases for which the reported cause of registration was ambiguous. Single-gene disorders accounted for at least 30% of all registered blindness.

We have now brought this review of records up to date, tabulating the new registrations for the past three years. We present here analyses comparing 1981 and 1984. We are also interested in the relative burden to the population of different causes of blindness, and therefore determined 'person-years of blindness' for the different categories as an index of the personal and population impact of each.

Patients and methods

The Canadian Province of Newfoundland and Labrador has a total population of approximately 580 000, the majority of whom live in relatively isolated, scattered coastal communities. The legal responsibility for the registration of blindness rests with the CNIB. Registration is not obligatory at present. The criteria for registration, only one of which need be met, are *(a)* corrected visual acuity of 6/60 or worse in the better eye, and *(b)* a total visual field of less than 10° from fixation using a white target 10 mm in diameter at a distance of 1 m.

The files of all persons registered on 31 December 1981 had previously been analysed in detail to determine the aetiological category.[2] Persons newly registered in each of the years 1980–4 have now been analysed in the same way. If there was some ambiguity in the diagnosis or aetiological code, an attempt was made to examine the patient. We have examined a total of 350 of the 1041 registered

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patients. In the case of retinal dystrophies and related conditions this examination included colour vision testing, dark adaptation, and electroretinography. Although glaucoma, diabetic retinopathy, and high myopia may have a strong genetic component, these entities were tabulated separately, not under established or presumed genetic disease.

The ages of death of all registrants dying in the years 1981–4 were obtained, as were their ages at registration. From these numbers were calculated the mean ages of registration for each major aetiological category, the duration of blindness to the nearest whole year of each deceased registrant, and the mean duration of blindness for each major aetiological category. For comparison the mean ages of registration for all registrants and for those first registered in the last five years were calculated. The determination of mean years of blindness is possible only for the period 1981–4, during which CNIB files have been monitored, as no continuing record is kept of age at registration and age at death of those deceased in earlier decades.

For each aetiological category we multiplied mean duration of blindness for deceased registrants (1981–4) by the overall number of patients in the category as at 31 December 1984 to arrive at 'person-years of blindness', an indicator of the relative burden to the population of each major cause of blindness.

Results

As at 31 December 1984, 1041 individuals were registered blind in the Province. Two hundred and fifty-three (24%) of these were blind because of single-gene disorders such as the retinal dystrophies, albinism, aniridia, or autosomal dominant cataracts, established by examination (Table 1). Another 5% were presumed to have genetic disorders on the basis of family history of such conditions as nystagmus or optic atrophy, but were not seen by us. The congenital group included some unidentified simplex cases of the genetic forms of cataract, coloboma, or microphthalmos. Senile macular degeneration (SMD), diabetic retinopathy, and glaucoma (each of which may be regarded as being multifactorial in aetiology), which are frequently noted elsewhere as leading causes of blindness, occurred much less often in this Newfoundland series than did monogenic blindness.

Between 1981 and 1984 there was only a small increase in the total number registered, from 1013 to 1041 (Table 1). The genetic and congenital proportions were unchanged, comprising over 40% of registrations. The proportions of myopia and glaucoma were also unchanged. There was an increase in the number of cases of senile macular degeneration. Blindness from infectious disease and trauma had decreased slightly in frequency. There were more deaths of elderly affected patients in these groups than new registrations. Fewer diabetics were registered now than previously; this reflects only imperfectly the high mortality in this group (see below).

Table 2 shows the registrations in each of the past five years. Except in 1983, when few diabetics were registered, senile macular degeneration, genetic conditions, and diabetic retinopathy were consistently the top three causes of registration.

The mean age at registration for the new registrants of the past five years was similar to that of the total registrations in each of the five major aetiological groups (Table 3). The mean ages of registration of

Table 1 *Causes of blindness in all persons registered with the Canadian National Institute for the Blind in Newfoundland and Labrador on 31 December 1981 and 31 December 1984*

	1981		*1984*	
	Number	*%*	*Number*	*%*
Genetic established	243	24·0	253	24·3
Genetic presumed	56	5·5	56	5·4
Congenital: cataract and multiple anomalies	110	10·9	116	11·1
High myopia	100	9·9	100	9·6
Senile macular degeneration	60	5·9	86	8·3
Infectious disease	88	8·7	77	7·4
Trauma and poisoning	67	6·6	62	6·0
Diabetic retinopathy	59	5·8	54	5·2
Glaucoma	48	4·7	49	4·7
Vascular and other systemic disease	41	4·0	42	4·0
Senile cataract	34	3·4	29	2·8
Tumour	22	2·2	21	2·0
Other	61	6·0	68	6·5
Undetermined	24	2·4	28	2·7
Total	1013	100·0	1041	100·0

Table 2 *Causes of blindness registration in each of the years 1980–4*

	1980	*1981*	*1982*	*1983*	*1984*	*Total*
Senile macular degeneration (SMD)	11	18	12	18	11	70
Genetic (established and presumed)	15	13	10	17	9	64
Diabetic retinopathy	15	11	10	3	13	52
Congenital	7	8	3	4	4	26
Glaucoma	3	6	3	8	3	23
Trauma and poisoning	5	7	5	1	2	20
High myopia	6	6	4	2	1	19
Vascular and other systemic disease	0	1	4	5	6	16
Senile cataract	5	3	2	3	2	15
Infectious disease	2	3	1	2	1	9
Tumour	1	0	1	0	1	3
Other and undetermined	7	4	5	6	3	25
Total	77	80	60	69	56	342

Table 3 *Mean ages at registration in five selected aetiological categories (years ±SD)*

	Total registration (n=1041)	New registrations 1980–4 (n=342)	Persons dying 1981–4 (n=175)
Diabetes	56 (±16)	53 (±18)	61 (±14)
SMD	74 (±9)	77 (±7)	77 (±7)
Glaucoma	62 (±17)	73 (±17)	71 (±12)
Myopia	46 (±16)	57 (±17)	58 (±11)
Genetic	25 (±16)	25 (±20)	46 (±19)

Table 4 *Mean years of blindness in five aetiological categories of those registered blind persons who died during 1981–4*

	Number of deaths	Mean age at registration	Mean age at death	Mean years of blindness
Diabetes	39	61	66	5
SMD	23	77	82	5
Glaucoma	15	71	81	10
Myopia	7	58	75	17
Genetic	22	46	67	21
		Total deaths 175		

Table 5 *Expected total 'person-years of blindness' in five aetiological categories, based on blind population registered on 31 December 1984*

	Number registered	Mean years of blindness	Person-years of blindness
Diabetes	54	5	270
SMD	86	5	430
Glaucoma	49	10	490
Myopia	100	17	1700
Genetic	309	21	6489

those who died within the past four years were also comparable, except for the genetic category; in this case the mean age of registration was 46 years, compared with 25 years for recent registrations and total registrations.

One hundred and seventy-five registrants died during 1981–4 (Table 4). The deaths in the diabetic retinopathy group were markedly out of proportion to their representation in the total sample; of 79 diabetics registered at some time during 1981–4, 39 died within that interval. During the same time 23 of 102 with senile macular degeneration died and only 22 of 326 with genetic conditions.

Persons with diabetic retinopathy and senile macular degeneration experienced on average five years of blindness, persons blind owing to high myopia 17 years, and persons blind due to monogenic conditions 21 years (Table 4). In the total registered blind population the 'person-years of blindness' attributable to diabetes were 270, to SMD 430, and to genetic diseases 6489 (Table 5).

Discussion

In analysing the records of all the registered blind persons in the Province our first goal was to determine as accurately as possible the underlying aetiology of the blindness. As has previously been discussed, in 15% of cases either the recorded cause of blindness or the aetiology code was found to be incorrect.[2] However, by undertaking this study in a geographic area with a relatively small and stable population we could establish family histories relatively easily and frequently examine patients with ambiguous records to establish diagnoses.

The high frequency of genetic blindness in Newfoundland is not a reflection of ascertainment due to our research interests. Rather than a recent increase in the proportion of monogenic blindness we are demonstrating a continued high prevalence. Single-gene disorders accounted for 30% of total blindness in our initial study in 1981, reflecting the high prevalence of this type of blindness over previous years.

The increase in senile macular degeneration in the 1981–4 interval may indicate improved ascertainment or a real increase as the life expectancy of the general population increases. In this interval there have been few new registrations in the categories of infection and trauma, presumably because of improved treatment, and the overall representation of these categories has decreased. New cases of blindness in younger people due to infection and trauma are unlikely to have escaped detection and registration in this well defined population. The cases which are more likely to escape registration at the appropriate level of vision are those due to slowly progressive diseases in older people—senile macular degeneration, diabetic maculopathy, and glaucoma.

It may be asked whether the high proportion of genetically determined blindness in Newfoundland is explained by the Province's population genetic structure. The population derives primarily by natural increase from settlers who arrived before 1835, drawn from highly circumscribed areas of south-western England and southern Ireland. Hundreds of small communities have grown up around Newfoundland's many natural harbours. At present about 50% of the population of the Province reside in communities of fewer than 2500 inhabitants, and 41% reside in communities of fewer than 1000. These small subpopulations remain genetically isolated (Bear JC, Nemec TF, Kennedy JC, *et al.*, unpublished data). The low levels of migration into these communities and of genetic exchange between them contrast with observations from numerous studies of European isolates of comparable size where there has been increasing genetic exchange in this century. Thus frequencies of specific recessive disorders may be increased owing to inbreeding. Because closely consanguineous unions tend to be avoided, the matings are usually between distant relatives, and the frequency of a recessive disorder is reasonably ascribed to founder effect (the chance presence of an allele in relatively few original settlers of a genetically isolated population). Several instances of locally raised frequencies of autosomal dominant and X-linked ocular disorders, such as von Hippel-Lindau disease and ocular albinism, have also been described, again reasonably attributed to founder effect. Conversely, just as some deleterious alleles are found in unusually high frequency, it is to be expected that some will be infrequent or absent, and indeed no examples of Best's macular dystrophy or of choroideraemia have been identified.

It must be emphasised that a high proportion of blindness due to hereditary disease is also indicated in studies elsewhere. In a county in Norway 29·6% of blind people (vision 6/60 or less) had hereditary or probably hereditary diseases.[3] Genetically determined conditions accounted for 77% of childhood blindness in Lebanon,[4] 79% in Cyprus (of which half were autosomal recessive),[5] and 84% in Saudi Arabia as already noted.[1] We have previously shown that the prevalence of genetic eye disease in Newfoundland was underestimated because of errors and ambiguities in coding at the time of registration of blindness.[2] This underestimation could also apply to other studies where it was not possible to review all files in detail or examine as many of the patients when there was ambiguity in the coding.

Persons with monogenic blindness, as a group, are registered much younger than other blind persons, and consequently have a much longer duration of blindness. Although the mean years of blindness calculated for the group of 22 who died in 1981–4 was 21 years, higher than for other groups, this none the less greatly underestimates the usual duration of monogenic blindness. The mean age of registration for the most recent registrants in the genetic group is 25 years (Table 3), not 46 years as in the small group who died recently. The mean years of blindness of the genetic group as a whole may therefore be expected to be around 42 years rather than 21 years and attributable 'person-years of blindness' about 13 000. Not only are monogenic conditions the leading cause of blindness, but also in 'person-years of blindness', the overall individual and population impact of monogenic blindness is overwhelmingly greater than that of other forms of blindness.

The mean duration of blindness attributed to SMD and diabetes was five years. Senile macular degeneration causes blindness primarily in elderly people with a short life expectancy. Although the mean age of registration for diabetics is lower, sometimes in the interval 20–30 years, life expectancy of this group is unfortunately very poor. In fact, of the 15 diabetics registered in 1980, 10 were deceased by 1985, compared with six of the 62 registered for other causes in 1980. Several young juvenile-onset diabetics died within one or two years of registration.

It is noteworthy that the genetic group appears to have a relatively low mean age of death (67 years), only one year higher than diabetics (66 years). If premature mortality among blind people with genetic disease is substantiated in studies of larger numbers of registrants, it will be important to try to determine what factors contribute to this. (Perhaps SMD and glaucoma registrants seem relatively long lived because these disorders are associated with advanced age.)

Regardless of the exact proportion of monogenic blindness in a particular country, the extra 'person-years of blindness' are relevant in all countries in which infectious and nutritional causes of blindness are adequately controlled. Moreover, the total genetic contribution to blindness extends well beyond the category of monogenic blinding disorders. Diabetes and glaucoma each show familial aggregation, and the genetic component in the liability to each is substantial. High myopia frequently seems strikingly familial.

While it remains of great importance to provide support through low-vision services, itinerant teachers for the visually impaired, and employment counselling, much more attention should be paid to elucidating the genetic component of blindness. This includes accurate diagnosis to provide specific recurrence risks for genetic counselling, clarification of the natural history and prognosis of individual disorders to provide specific advice for affected persons, and genetic linkage studies, to allow carrier detection and presymptomatic identification of affected individuals.

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Blindness and partial sight in an elderly population

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SUMMARY A cross sectional, prevalence survey of eye disease in the population over 75 years old of Melton Mowbray has been used to examine the accuracy and completeness of the Blind and Partially Sighted Registers. The Blind Register had high sensitivity and specificity but was found to underestimate the prevalence of blindness by a factor of 1·1. The Partially Sighted Register had high specificity, but the sensitivity was only 50% and it underestimated the prevalence of partial sight by a factor of 1·5. Seven persons eligible for registration, but previously not registered, were found, two as blind and five as partially sighted. This represented 21% of the registrable visually impaired population.

In the United Kingdom the placement of visually handicapped persons on the Blind and Partially Sighted Registers is not compulsory. Registration depends on having a certificate of blind registration (form BD8 in England and Wales) completed by a consultant ophthalmologist.

The definition of blindness for the purpose of registration is 'so blind as to be unable to perform work for which eyesight is essential'. Although there is no statutory definition of partial sight in the 1948 National Assistance Act, the Ministry of Health subsequently advised that a person who is not blind within the meaning of the Act, but who is 'substantially and permanently handicapped by defective vision caused by a congenital defect, illness or injury' is eligible to be registered as partially sighted.[1]

Persons registered as partially sighted may receive the same welfare services as are provided by the local authorities for the blind but are not eligible to receive other benefits specifically enjoyed by the blind, such as income tax concessions and supplementary benefit.

Since registration as blind or partially sighted is entirely voluntary, there is no method of ascertaining whether all those eligible for blind registration are so registered. Studies[2-4] have suggested that the Blind and Partially Sighted Registers may seriously underestimate the number of visually handicapped persons in the community.

In this report we present the results of a survey of eye disease in a defined, elderly population in England, which has been used to examine the Blind and Partially Sighted Registers. The main purpose of the study was to determine accurately the amount of unregistered blindness and partial sight in an elderly population. A considerable amount of data were obtained about the visual acuity in the elderly and they are also presented in this report.

Materials and methods

Melton Mowbray is a market town in Leicestershire, England, that lies midway between the cities of Leicester and Nottingham. An unusual situation exists in Melton Mowbray in that virtually the whole population of the town and surrounding rural district is served by a single, 12-doctor general practice. The practice population (32 000 persons) is virtually identical with the geographically defined population of Melton Mowbray, and since 1980 has been established on a computerised age-sex register.

In 1981 the Department of Community Health, Leicester University, carried out a comprehensive household survey of all persons aged 75 years and over on the age-sex register. This survey was concerned with all aspects of health and social services.[5] The surviving members of this cohort still living in the town and surrounding rural area of Melton Mowbray on 1 April 1982 formed the target population for a study of the prevalence of eye disease in the elderly. The basis and preliminary results of this study have been reported elsewhere.[6]

The study population were listed in random order from the age-sex register and over a two-year period were asked to attend a special eye clinic which had

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been set up for the purposes of this study. Each attender underwent a full examination by an ophthalmic optician (JRL) and an ophthalmologist (JMG).

A total of 677 persons were available for examination at the time the study was initiated, and 529 persons attended and took part in it, a response rate of 78·1%. Each person attending the eye clinic underwent a full ophthalmic examination, including fundus examination and photography, after pupillary dilatation. Distance visual acuity was measured by a standard illuminated Snellen test chart at a measured distance of 6 metres. Near vision was ascertained with a test type approved by the Faculty of Ophthalmologists. Vision was tested with and without spectacles, if worn, and after refraction with the appropriate correction. Subjects were referred to Leicester for formal visual field examination only if suspected of having open-angle glaucoma. Four hundred and seventy-four persons (90% of participants) attended the eye clinic at the War Memorial Hospital in Melton Mowbray and had a full ophthalmic examination. Fifty-five persons were examined at home, in nursing homes, or in hospital.

The Royal Leicestershire, Rutland, and Wycliffe Society for the Blind kindly provided an up-to-date list of all persons aged 75 years and over, living in the defined area of Melton Mowbray and surrounding villages, who were registered blind or partially sighted. The society also made available the completed BD8 forms for confidential examination, from which information including visual field data was recorded.

Results

The corrected distance visual acuity after refraction is presented for the 474 study participants by better eye in diagrammatic form in Fig. 1. The data for the 55 persons who were examined under non-standardised conditions at home or in hospital have been excluded from analysis. Eighteen persons (3·8%) were found to have corrected visual acuity of 6/60 or less in their better eye, and 11 of these had been previously registered, nine as blind and two as partially sighted. One hundred and twenty-two persons (25·7%) had corrected vision of less than 6/18 in their better eye, and therefore can be defined as visually impaired under the classification of the World Health Organisation.[7]

The data for corrected binocular near vision of 474 study participants is presented in diagrammatic form in Fig. 2. Over three-quarters of the participants had corrected binocular near vision, of N6 or better. Fifty-eight persons (11·1%) had corrected binocular vision of less than N8, which is usually considered the size of normal book print.

The binocular near vision of the 55 non-ambulatory participants, who were examined at home and in hospital, are presented in Fig. 3 for comparison. Nineteen persons (35%) had corrected binocular vision of less than N8.

BLIND REGISTER

Analysis of the Blind Register relating to patients from Melton Mowbray and its surrounding villages

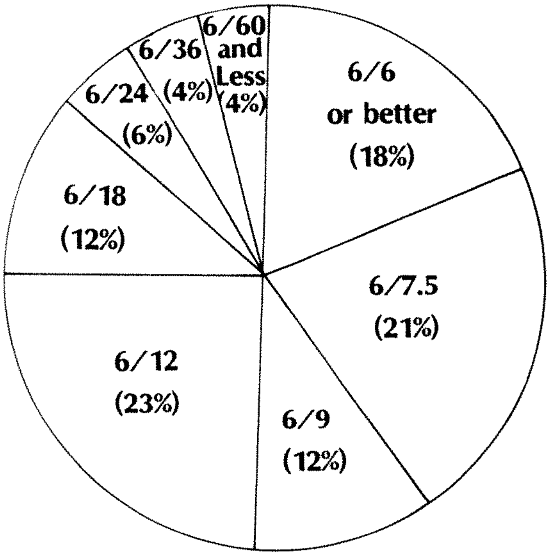

Fig. 1 *Corrected distance visual acuity of study participants by better eye for the sample examined under standard conditions (474=100%).*

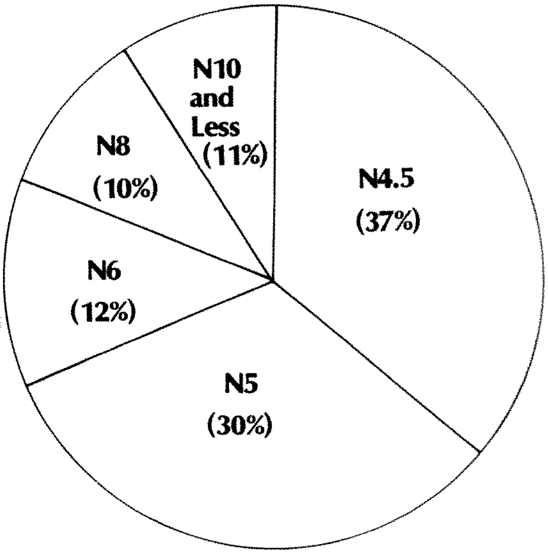

Fig. 2 *Corrected binocular near vision of study participants, for the sample examined under standard conditions (474=100%).*

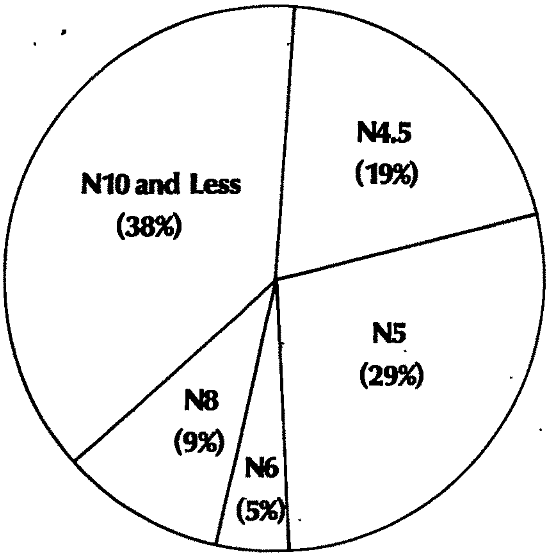

Fig. 3 *Corrected binocular near vision for non-ambulatory study participants (55=100%).*

Table 1 *Study participants registered blind: comparison of data from BD8 and eye study*

Information from BD8 forms				*Information from survey*	
Case	*Diagnosis*	*Field of vision*	*Corrected vision in better eye*	*Corrected distance vision better eye*	*Binocular near vision*
1	AMD	Central scotoma	HM	CF	N48
2	AMD, OAG	<10°	6/60	6/18	N8
3	AMD	Contracted	6/24	6/18	N5
4	Cararact, diabetic retinopathy	<10°	HM	6/9	N6
5	Cataract	Contracted	CF	6/12	N9
6	CRAO	Central scotoma	CF	HM	<N48
7	AMD	Central	CF	CF	<N48
8	OAG	<10°	CF	6/60	N24
9	Cataract, ACG	Central scotoma	CF	PL	<N48
10	Corneal scar	Contracted	NPL	6/36	N36
11	AMD	Central scotoma	CF	CF	N24
12	AMD	Central scotoma	CF	CF	<N48
13	AMD	Central scotoma	CF	CF	N48
14	AMD, cataract	Central sctoma	CF	6/60	N8
15	AMD	Central scotoma	CF	6/24	N5

AMD=age-related macular degeneration. OAG=open-angle glaucoma. CRAO=central retinal artery occlusion. ACG=angle closure glaucoma.

showed that 15 persons aged 75 years and over who had participated in the study were registered as blind. The details of the visual acuity, field of vision, and diagnosis at registration obtained from the BD8 forms are presented in Table 1 and compared with the survey findings.

In terms of age and sex ratio those persons registered as blind were similar to the study participants as a whole.

PARTIALLY SIGHTED REGISTER

Eleven persons in the study population were registered as partially sighted, and the details of the visual acuity, field of vision, and diagnosis at registration of these persons are presented in Table 2, with the survey findings included for comparison.

The sex ratio and the mean age of these persons were not significantly different from those of the study participants as a whole.

UNDETECTED VISUAL HANDICAP

In the survey seven persons were found who had corrected visual acuity 6/60 or worse in their better eye but had not previously been registered as blind or partially sighted. This number represented 21%

Table 2 *Participants by partial sight registration: BD8 and survey data*

Information from BD8 forms				*Information from survey*	
Case	*Diagnosis*	*Field of vision*	*Corrected vision in better eye*	*Corrected distance vision better eye*	*Binocular near vision*
1	Cataract, CRVO AMD	Central scotoma	6/24	HM	<N48
2	AMD, CVA	Hemianopia, central scotoma	6/24	CF	N48
3	Cataract, CRVO, AMD	<10°	6/36	6/36	N8
4	Cataract	<10°	6/24	6/24	N8
5	Cataract, AMD	Central scotoma	6/60	6/36	N8
6	AMD	Central sotoma	6/36	6/36	N9
7	AMD	Central scotoma	CF	6/24	N9
8	AMD	Central scotoma	3/60	6/36	N18
9	Cataract	Central scotoma	6/36	6/24	N8
10	OAG	Contracted	6/36	6/18	N8
11	Cataract, AMD, RD	Full	6/60	6/24	N4·5

CRVO=central retinal vein occlusion. AMD=age related macular degeneration. CVA=cerebrovascular accident. RD=retinal detachment.

Table 3 *Participants with undetected visual handicap*

Case	*Age in years*	*Sex*	*Corrected distance V/A*	*Binocular near V/A*	*Diagnosis*
1	83	F	6/60	N18	AMD
2	82	F	6/60	N14	AMD
3	83	F	6/60	N12	AMD
4	82	F	6/60	N6	Cataract/ amblyopia
5	87	F	6/60	N9	Cataract/ ACG
6	86	F	CF	<N48	AMD
7	92	F	CF	<N48	AMD

(7/33) of all persons registrable as blind or partially sighted in the study, and their visual acuities and diagnoses are presented in Table 3.

Discussion

In his reports on blindness and partial sight in England and Wales Sorsby observed that these registers probably seriously underestimated the true prevalence of blindness and partial sight in the population.[8] Since there are less obvious financial benefits for those registered as partially sighted, it is generally suspected that the Blind Register is more complete than the Partially Sighted Register.

Several studies have examined the accuracy of the Blind and Partially Sighted Registers. Graham and coworkers[2] assessed registrable blindness in a 1600-patient group practice in Wales, by means of a postal survey and follow-up examination of a random sample of participants. Although the visual criteria considered necessary for registration were not presented, they found that nine of 31 blind persons were not on the Blind Register. Brennan and Knox[3] studied the accuracy and variability of the Blind Register in England by reviewing data derived from local authority returns to the Department of Health and Social Security. They found that there was a wide variation in the prevalence of blind and partial sighted registrations between different areas, which could not be accounted for by differences in age or socioeconomic features. They concluded that these variations were accounted for by differences in registration procedures and that the true prevalence of blindness was higher than that shown on the register by a factor of from 1·1 to 1·4. For the Partially Sighted Register they suspected that this ratio must be even greater.

Cullinan[4] has performed surveys of visually handicapped persons in Canterbury and also on a wider scale in England and Wales. In his report he provides a comprehensive review of the literature and suggested that the Blind Register underestimates the true number of persons potentially eligible for registration by about 30%, and the Partially sighted Register did so by approximately 20%.

The major problem confronting any assessment of the accuracy of the Blind and Partially sighted Registers is the absence of exact visual acuity criteria in the definitions of blindness and partial sight. It should be remembered, however, that the main purpose of these registers is the identification of persons for whom welfare measures might be undertaken, and not for medical research. In this context, therefore, it is a positive advantage not to have rigid visual acuity conditions in the definitions, since their absence preserves a flexibility for registration that is probably beneficial.

Nevertheless for the purpose of considering the accuracy and completeness of these registers the lack of exact criteria is a significant problem. In fact clear guidelines are laid down in the form BD8 on the visual acuity requirements for registration. In general terms a person may be registered as blind if there is a corrected visual acuity of 3/60 or worse in the better eye; or with corrected vision of 3/60 but less than 6/60 with a contracted field of vision; or if the corrected vision is better than 6/60 but the visual field is markedly restricted. For partial sight registration the conditions are: a corrected visual acuity of 3/60 to 6/60 with full visual field, in the better eye; or a visual acuity of up to 6/24 with moderate constriction of the field; or 6/18 and better corrected vision in the better eye with a gross visual field defect.

Using these visual acuity criteria, we found that seven persons who were previously 'undetected' were eligible for registration by consideration of the corrected distance visual acuity alone. Two of this number could be considered registrable as blind, since the corrected visual acuity was only counting fingers at 1 metre, while the remaining five persons would be eligible for partial sight registration. These details are presented in Table 3. The Blind Register therefore apparently underestimated the true prevalence of blindness in the sample by a factor of 1·1 (17/15), while the Partially Sighted Register did so by a factor of 1·5 (16/11).

It would perhaps be dangerous to extrapolate these findings to the population of England and Wales as a whole. One reason for this is that these figures were based on only the qualifying central visual acuity as described above, and did not take into account visual field examinations, which were performed in the study only on glaucoma suspects. This lack of consideration of visual field data might underestimate the true prevalence of blindness and partial sight but only to a very small degree.

Although the original sample was randomly chosen, our study participants were in fact volunteers and therefore self-selected and may not have been representative of the study population as a whole. However, information about the visual status of the 148 non-responders was obtained from two sources —the original Household Survey Data[5] and from the Blind and Partially Sighted Registers. In the Household Survey participants were asked if they had any visual difficulty at the time of the survey (1981–2). 6% of the Eye Study participants and 14% of the non-participants admitted to some form of difficulty with vision, and this difference was statistically significant ($p<0\cdot001$). More importantly, 10 of the non-responders were registered as blind and six as partially sighted. Of the non-responders, therefore, 16/148 were registered compared with 26/529 of the study participants, a marked discrepancy.

These figures suggest that the prevalence of blinding eye disease was higher for the non-responders than for the study participants. Therefore our figures should perhaps be regarded only as indicators of the minimum likely prevalence of undetected blindness and partial sight.

In fact the amount of visual disability in the elderly population at large is probably much greater than would be expected from clinic measurements, since the level of vision obtained in the clinic, after refraction, is probably considerably better than the functioning vision of these persons at home. Cullinan and others[9] have already pointed out that for elderly, visually handicapped subjects clinic visual acuity measurements can often be misleading compared with home measurements.

Consideration of Tables 1 and 2 reveals a wide variation in recorded visual acuities between those measured for the purposes of registration and those obtained in the survey. Since both values were for corrected vision by better eyes, it is somewhat surprising that such large differences should occur, since in most of the cases one would only have expected a deterioration in vision in the period between completion of form BD8 and examination in the study.

Inspection of the study data shows that, in persons with visual handicap, there is little apparent correlation between corrected distance acuity and corrected binocular near vision. This has also been noted by Cullinan.[4] Since form BD8 is under review, it is perhaps an opportune moment to consider whether attention should be given to near as well as distance acuity measurements.

Despite the discrepancies in visual acuity measurements between registration and survey measurements, only two persons could be considered to be falsely registered on the Blind Register on the above-mentioned criteria (Table 1). The two participants in question (numbers 14 and 15) were found in the survey to have corrected visual acuity for distance, outside the usually accepted levels for registration as blind. In addition they both had full peripheral fields.

Table 4 *Sensitivity and specificity of Blind register*

	Registrable as blind	*Non-registrable*
Registered as blind	(a) 13 (True positive)	(b) 2 (False positive)
Not registered as blind	(c) 2 (False negative)	(d) 457 (True negative)

$$\text{Sensitivity of Blind Register} = \frac{a}{a+c} = 87\%$$

$$\text{Specificity of Blind Register} = \frac{d}{b+d} = 99\cdot6\%$$

For the Partially Sighted Register, however, at least six persons (numbers 6–11) appear to fall outside the usual criteria for registration. More importantly, two persons (1 and 2) were found to have sufficient visual handicap to be eligible for full blind registration.

When considering the accuracy of any screening test it is important to measure the extent to which a test measures what it purports to measure. Although the Blind and Partially Sighted Registers cannot be considered as methods of screening for visual disability in the population, it is nevertheless appropriate that the specificity and sensitivity of the registers be considered. The sensitivity of a test is a measure of its ability to detect true positive values of a particular variable, while the specificity is a measure of its ability to detect true negative values.

For the Blind Register 15 persons were registered of whom 13 could be regarded as fulfilling the visual criteria (true positives) and two who did not meet these criteria (false positives). In addition two persons were registered as partially sighted who were eligible for blind registration (false negatives). The calculations of specificity and sensitivity are illustrated in Table 4 and show that for the Blind Register the sensitivity was 87%, while the specificity was over 99%. For the Partially Sighted Register, however, these measurements are not so reassuring. Five persons were found to fulfil the visual criteria (true positives) and a further five were unregistered (false negatives). Six persons who were registered were found not to fulfil the visual criteria. The calculation of sensitivity and specificity are illustrated in Table 5. The sensitivity of the Partially Sighted Register was only 50%, but specificity was almost 100%.

The findings of this study and others suggest that the true prevalence of visual handicap is greatly underestimated in the registration of the partially

Table 5 *Sensitivity and specificity of Partially Sighted Register*

	Registrable as partially sighted	*Non-registrable*
Registerd as partially sighted	(a) 5 (True positive)	(b) 6 (False positive)
Not registered as partially sighted	(c) 5 (False negative)	(d) 458 (True negative)

Sensitivity of Partially Sighted Register $= \frac{a}{a+c} = 50\%$

Specificity of Partially Sighted Register $= \frac{d}{b+d} = 99\%$

sighted, while that of the blind is remarkably accurate. It should be emphasised that the main purpose of both the Blind and Partially Sighted Registers is social rather than statistical. Indeed the wide variation of visual acuity recordings between the survey and forms BD8 suggests that both registers are far from ideal for research purposes. Most ophthalmologists and others concerned in the welfare of the visually disabled will welcome the fact that the BD8 registration form is under review. The inclusion of a near vision test as an extension of visual assessment for disability could be a useful addition.

We acknowledge the help and co-operation of the general practitioners of Latham House Medical Practice, Melton Mowbray, for permission to approach their patients and carry out this study. Mr Philip Parkinson of the Royal Leicestershire, Rutland, and Wycliffe Society for the Blind kindly made available completed BD8 forms for confidential examination and also commented on the manuscript. Professor Michael Clarke, Department of Community Health, Leicester University, provided expert comment on aspects of the paper, and it is a pleasure to acknowledge the help of Mrs Jill Wood, who prepared the final manuscript.

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Prolactinoma presenting with intermittent third nerve palsy

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SUMMARY A patient presented with a painful third nerve palsy. This resolved spontaneously, but recurred several months later. At his second presentation carotid angiography gave normal results, but a high resolution CT scan showed a tumour in the right parasellar region. The serum prolactin was raised at over 22 000 mμ/, showing this to be a prolactinoma.

A prolactinoma is not normally considered as a diagnosis in cases of painful third nerve palsy, the common causes being intracranial aneurysm, herpes zoster ophthalmicus, temporal arteritis, and migraine. A review of the literature revealed only one case report of a third nerve palsy caused by a prolactinoma, but that was neither isolated nor intermittent.[1] However, pituitary tumours have been known to cause third nerve palsies before the diagnosis of prolactinoma was feasible. The unusual feature of the following case report, therefore, is that the patient's third nerve palsy was intermittent.

Case report

A 74-year-old woman presented in June 1983 with a right sided headache of five days' duration, an increased prominence of the left eye, and diplopia in all directions. Her previous medical history included thyrotoxicosis diagnosed in 1964 for which she was initially treated with carbimazole (Neo-Mercazole) followed by a subtotal thyroidectomy. Dysthyroid exophthalmos and lid retraction of the left eye were noted at that time and had persisted since then. In 1972 the patient was found to be hypertensive, and antihypertensive treatment was begun.

Clinical findings on presentation in June 1983 consisted of 3 mm proptosis and lid retraction of the left eye, this appearance being exaggerated by a right ptosis, associated with a dilated right pupil with no direct or consensual response to light or accommodation, and paralysis of the right medial, superior, and inferior recti, with no evidence of function of the inferior oblique. The fourth and sixth nerves were intact, and there were no other abnormal findings in the cranial nerves. In particular the visual fields were normal.

The patient was admitted immediately to hospital for bed rest and investigation of a possible right sided intracranial aneurysm. The ptosis and mydriasis cleared during the following week and the diplopia ceased, so that when reviewed by a neurologist on 13 July 1983 the patient was asymptomatic, and the only neurological finding was a 3 mm proptosis of the left eye. At this stage the neurologist did not consider that further investigation was justified.

Ten months later, in May 1984, the patient had an episode of weakness affecting her left arm for three hours and some intermittent numbness of her face. Her erythrocyte sedimentation rate (ESR) at this stage was 55 mm/h.

Within one month her right third nerve palsy returned, with increasingly severe right sided headache. The movements of the right eye were again severely limited, with a dilated pupil and partial ptosis. Carotid angiography was undertaken, but no aneurysm was seen. The possibility of the recurrent third nerve palsy and the transient ischaemic attack both being due to temporal arteritis was considered, although the highest ESR recorded was 57 mm/h. However, a temporal artery biopsy specimen in November 1984 was normal. A high resolution CT scan of the orbit showed an enhancing lesion in the right parasellar region, with erosion of the right side of the dorsum sellae, which was displaced backwards. Scans through the pituitary fossa showed a tumour occupying the right side of the fossa and extending into the parasellar region. The floor of the fossa was thinned, with extension into the sphenoid sinus and backwards into the dorsum sellae (Fig. 1).

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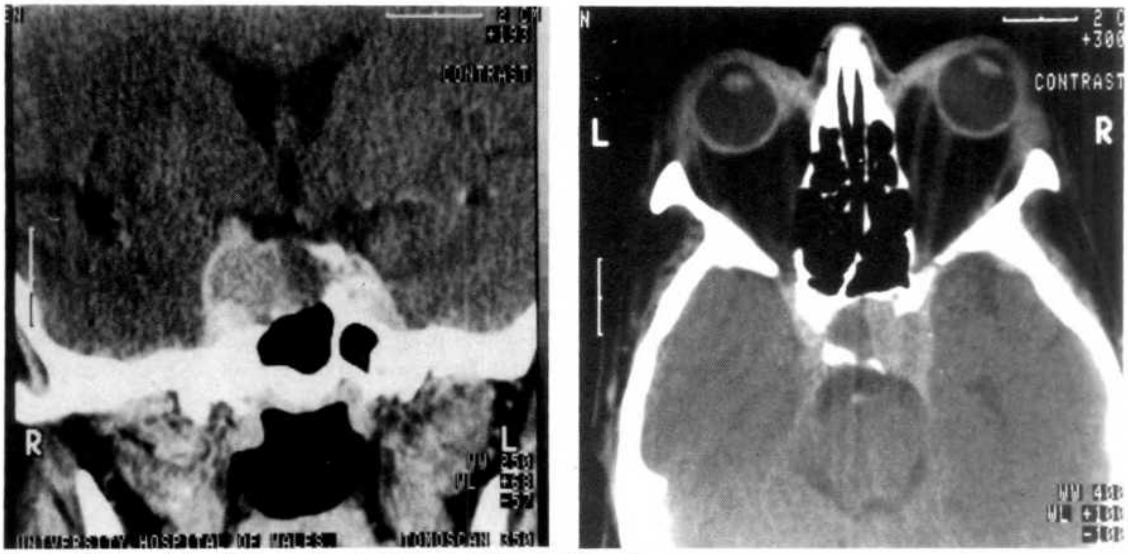

Fig. 1 *High resolution CT scans showing lesion in right parasellar region.*

It was considered at this stage that the appearance was most probably due to a malignant tumour, and therefore a course of radiotherapy was started. However, endocrine investigations showed a grossly raised prolactin level of over 22 400 mμ/1. Following radiotherapy the patient's prolactin level was greater than 5000 mμ/1, and a second CT scan showed no change. Treatment was changed to bromocriptine, which is known to be effective in reducing the size of prolactinomas.[2,3] The patient had been on bromocriptine for two months at the latest review, but with no change in the signs.

Discussion

A review of the literature revealed only one case where a prolactinoma was associated with a third nerve palsy.[1] In that case the prolactinoma of a 51-year-old woman had extended superiorly and laterally, causing both bitemporal visual field defects and a cavernous sinus syndrome. The patient recovered over a period of six months on bromocriptine therapy.

Prolactinomas commonly present in women in early reproductive life with problems of infertility, though they may present with any type of menstrual abnormality.[4,5] Galactorrhoea may also occur (in 30–80% of cases).[5,6] When the tumour presents as an expanding lesion, it usually causes visual field loss (in 7% of female cases).[5] Men present later with impotence and obesity.[7,8] However, our patient presented with a painful third nerve palsy, which was exceptional for being isolated and in particular for being intermittent.

I thank Mr A G Karseras, consultant ophthalmologist, for his help and encouragement in preparing this paper.

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Intraoperative keratometry with the oval comparator (astigmometer)*

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SUMMARY The Astigmometer is a simple accessory which is attached to a surgical microscope. It allows precise suturing of the cataract wound and reduced the amount of postoperative astigmatism at six weeks. This allowed rapid visual rehabilitation and more active patients. It obviated the removal of sutures in the postoperative period in most patients (90%). However, stable results after one year were obtained with selective suture cutting without the use of intraoperative keratometry. This was almost as good as in the astigmometer group, but the percentage of astigmatism less than 1 dioptre was reduced and that greater than 2 dioptres was increased.

With the advent of the intraocular lens and extended wearing of contact lenses rapid return of good vision without spectacles is possible if minimal astigmatism has been induced by the surgeon. Many authors have reported attempts to minimise postoperative astigmatism by using modified surgical techniques or the use of measuring devices to determine the amount of astigmatism induced on the operating table by the sutures.[1-3] The most detailed reports are those describing the use of the Terry keratometer.[4-6] However, the cost, complexity, and difficulty in using this system has prevented more universal acceptance.

An attempt was made to develop a new type of instrument to determine intraoperative astigmatism and set up the wound so that the natural wound slippage would return the cornea to a near perfect shape.

Theory and description of astigmometer

The light source is a circular arrangement of high-intensity light-emitting diodes attached to the operating microscope body. A self-illuminating ring in the focal plane of one eyepiece is rotated about its axis by means of a dial with a sterilisable cover. The oval produced is matched to that of the reflected light ring produced by the anterior corneal curvature. By means of the principle of concentric or superimposed ovals a reading can be made.

When a circular ring of lights is reflected from the surface of the cornea, an estimation of the corneal astigmatism existing at that time can be made. If the incision is approximated too loosely, there is gaping of the wound edges. The radius of curvature, therefore, in the vertical meridian is longer than the radius of curvature in the horizontal meridian. This causes a 'flattening' of the cornea vertically and results in an 'against the rule' astigmatism. An elliptical reflex with the longer axis directed vertically demonstrates an 'against the rule' astigmatism (Fig. 1).

If the incision is closed too tightly, there is compression of the wound. The radius of curvature of the cornea in the vertical meridian becomes shorter than the radius of the curvature in the horizontal meridian. This causes a 'steepening' of the cornea vertically and results in a 'with the rule' astigmatism. An elliptical reflex with its shorter axis directed vertically shows a 'with the rule' astigmatism (Fig. 2).

Fig. 3 shows a standard operating microscope eyepiece which has been modified to include the 'Ovalometer'. It is an elegantly simple device that consists of nothing more than an illuminated ring member rotating about its axis in the focal plane of the eyepiece. This is illustrated by the circle of rotation of the circular member round its anchoring and rotatory shaft, which acts as a pivot. The focal plane of the eyepiece is the plane in which the viewed object is brought to focus. It is here that the surgeon sees the image of the circular ring of lights after it has

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*Presented at the American International IOL Congress, Boston, Mass, 12 April 1985.

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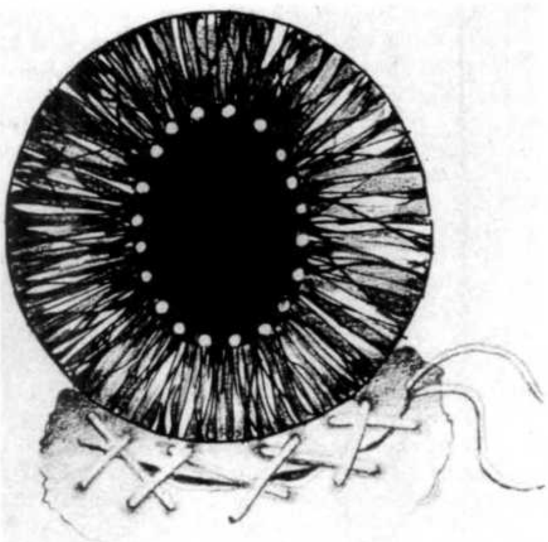

Fig. 1 *Vertical reflected ring of light demonstrating 'against the rule' astigmatism. Suture too loose.*

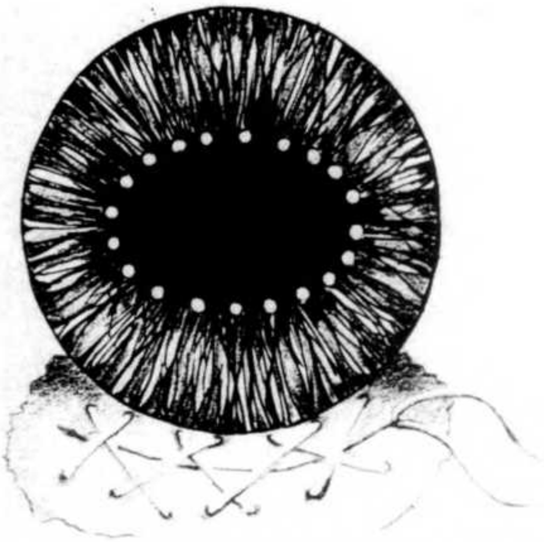

Fig. 2 *Horizontal eliptical reflected light ring showing 'with the rule' astigmatism. Suture too tight.*

been reflected back by the anterior surface of the cornea acting as a convex mirror. It should be emphasised that any difference in the horizontal and vertical axis of the cornea will change the reflection of this circular ring of lights into an oval appearance.

Fig. 4 illustrates the mathematical relationship of the ring as it is rotated about its pivot and/or the ovals produced as seen by the surgeon looking in the direction of the large arrow. If the image of the inner circle of the viewing ring is projected on to the horizontal line, it makes a right angle with the plane. A triangle with a right angle has a hypotenuse, an adjacent side and an opposite side. The projected image seen in the focal plane is the adjacent side in a triangle and its length is defined by angle α. Its length is calculated by the simple formula of cosine α multiplied by the length of the hypotenuse. As it is rotated from position 1 to position 2 it shortens as angle α increases. The hypotenuse represents 43

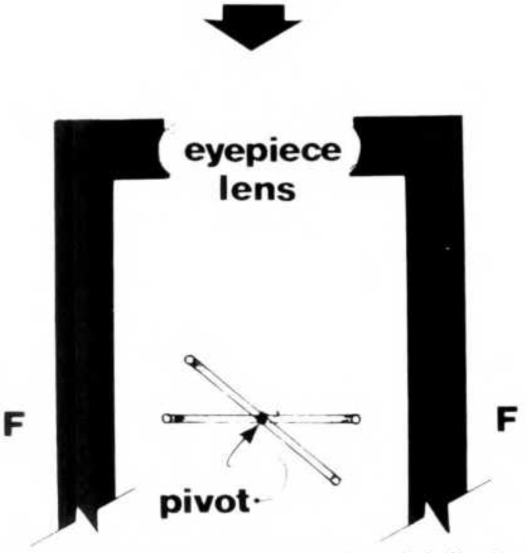

Fig. 3 *Microscope eyepiece modified to include illuminated astigmometer showing rotation about its pivot.*

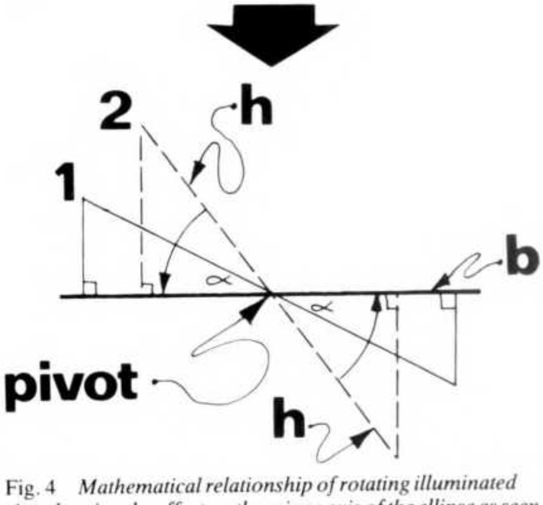

Fig. 4 *Mathematical relationship of rotating illuminated ring showing the effect on the minor axis of the ellipse as seen by the surgeon looking into the eyepiece.*

dioptres of power or a radius of curvature of 7·8 mm. The amount by which astigmatism varies according to the angle of rotation of the illuminated ring in the eyepiece at the focal plane is shown. For example, a rotation of 17° is equal to an astigmatism of 2 dioptres; a rotation of 20° is equal to 2½ dioptres; a rotation of 21.5° is equal to 3 dioptres, and a 25° rotation produces 4 dioptres of astigmatism. If the axis is not horizontal, the long axis of the pivot is moved by rotating the eyepiece.

Subjects and methods

This prospective study included 200 consecutive cases of routine extracapsular cataract extraction with implantation of a posterior chamber lens. In 50 eyes wound closure was performed without the use of an astigmometer and on 150 such a device was used.

An identical surgical technique was attempted in all cases, especially as regards the site and size of the incision. A 12 mm arc (10 mm chord) three-plane incision was made, starting 1–1½ mm posterior to the surgical limbus, with a diamond knife. The flap was dissected with a hockey stick knife until well into clear cornea. The cornea was entered with a diamond knife and the incision enlarged with scissors (Fig. 5).

The wound was closed with a 9-0 nylon suture. This started on the scleral side at the right, and five crosses were made by the suture passing through the incision to the left and then back to end in the right corner of the wound. As the needle ended the suture on the corneal side of the incision on the right, the knot was tied so that it buried itself in the wound. The suture bites included the entire depth of the corneal flap; they started deep into the sclera under this flap, extended its whole width, and came out in intact sclera 1 mm distal to the first plane of the incision.

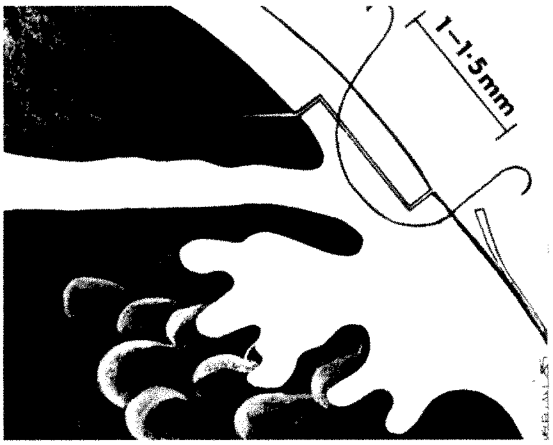

Fig. 5. *Cross-section of eye showing surgical wound site and suture location.*

Before the astigmometer was used a single triple-throw tie was made and the anterior chamber inflated with balanced salt solution (BSS). The intraocular pressure was set at between 15 and 25 mmHg with a hand held plastic tonometer. The ring of light was placed directly on the apex of the cornea. Speculum contact with the eye was removed and the bridle suture released. In most cases a Schott speculum was used, and this prevented any pressure on the eye. The suture was adjusted to produce approximately 3 dioptres of astigmatism with the rule. If this required more than one attempt at loosening the suture, the eye was reflated with BSS every time and the intraocular pressure checked. If tightening of the suture was required for the procedure, the eye was slightly softened by an anterior chamber tap and then the suture pulled up, with repeated monitoring of the intraocular pressure.

The keratometer reading was taken preoperatively, 18–24 hours after surgery, and then six weeks and thereafter for one year. A Nikon keratometer using the Helmholtz principle of doubling was used in all cases. Careful suture cutting was begun at six weeks in cases of severe astigmatism greater than 2 dioptres. This was performed at weekly stages, as steroid drops were used in the first four weeks postoperatively, with weak steroid drops continued for two months. These readings were used to determine the amount of preoperative and postoperative corneal astigmatism as well as the astigmatic decay that occurs during the postoperative phase.[3]

Results

Table 1 shows a comparison of the astigmatism in the two groups. The results at the six-week interval before suture removal show a significant difference between the groups using the astigmometer and the control group (Table 2). The mean six-week postoperative astigmatism was 1·08 dioptres in the astigmometer group and 3·41 dioptres in the control group. Selective suture cutting was then begun in the control cases and astigmometer cases where the astigmatism was greater than 2 dioptres. This was done in one to three stages at weekly intervals. Only 6% of the astigmometer group had astigmatism greater than 3 dioptres six weeks after surgery as compared with 30% of the control group, and

Table 1 *Preoperative astigmatism (200 cases)*

Dioptres	*Percentage*
0 to 1	68%
>1 to 2	21%
>2 to 3	8%
>3	3%

Table 2 *Postoperative astigmatism six weeks after surgery, before suture removal*

Astigmatism (dioptres)	*Control (50 eyes)*	*Ovalometer (150 eyes)*
0 to 1	16 (32%)	91 (61%)
>1 to 2	10 (20%)	44 (29%)
>2 to 3	9 (18%)	9 (6%)
>3	15 (30%)	6 (4%)

changes of up to 10 dioptres were found in the latter group (Table 2). The mean astigmatic change from the astigmometer readings during surgery was 2·96 dioptres in the first six weeks. This figure shows a mean keratometric decay of almost 3 dioptres with the rule in this period. It illustrates a stretching or slipping of the wound in the vertical meridian of 7%, represented by the difference of the y and x axis of the oval as measured by the astigmometer.

Discussion

The data show the great difference in postoperative astigmatism between the two groups of cases after six weeks. The wound slippage of 7% in the first six weeks is clearly illuminated by the data obtained from the astigmometer group. Clearly the wound stretching occurs at right angles to the centre portion of the cataract incision, and this is confirmed by the astigmometer findings. It is almost certainly influenced by the concentration and duration of the steroid used. All cases done had a subconjunctival injection of methylprednisolone acetate (Depo-Medrol) at the end of surgery (0·3ml) as well as six weeks of dexamethasone 0·1% (Spersadex) drops, and 95% were given prednisolone acetate 1% (Pred Forte) drops during this period. Steroids were continued for another six weeks, but weaker concentrations were used, namely flurometholone 0·1% (FML).

The cornea can be likened to a ball that has been distorted by the sutures compressing the wound. Its elastic modulus and intraocular pressure attempt to restore its original shape, which is prevented by tight sutures but aided by all factors which delay wound healing. In all cases of astigmatism greater than 2 dioptres the sutures were carefully cut in stages starting with the suture at the extreme end of the wound nearest to the knot. This was followed by the suture at the other end of the wound in one week and then one or two central cuts, a week later, if required.

The reason only 50 cases were done as a control as compared with the 150 cases on the astigmometer is that the latter patients were so much happier that the use of further controls was thought to be ethically unjustifiable. The ability of the surgeon to measure the tightness of his suture line will certainly allow him to improve his individual technique.

The results after one year showed much less difference in the amount of astigmatism (Table 3). This finding shows that with great care in the cutting of the suture in cases of excess astigmatism good results can be obtained. The percentage of cases with small (less than 1 dioptre) astigmatism, however, is reduced, and the percentage of astigmatism greater than 2 dioptres is increased.

Table 3 *Astigmatism: 12 months after surgery*

Astigmatism (dioptres)	*Control (50 eyes)*	*Ovalometer (150 eyes)*
0 to 1	26 (52%)	87 (58%)
>1 to 2	16 (32%)	48 (32%)
>2 to 3	4 (8%)	9 (6%)
>3	4 (8%)	6 (4%)

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Cryosurgery for trichiasis in black patients

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SUMMARY A total of 34 lids with aberrant lashes were treated with the specifically designed Collin cryoprobe without microthermocouple temperature monitoring. A high success rate of 82% was obtained. By applying the cryoprobe to the lid margin and conjunctival surface instead of to the skin it was possible to limit the degree of depigmentation in these highly pigmented lids, and only one patient showed a mild cosmetic blemish. The treatment was repeated on up to three occasions without an increase in complications.

Cryotherapy has become accepted as a successful form of treatment in trichiasis,[1-4] especially if a large number of aberrant lashes are present.[5] The initial experimental work and clinical trials were described by Sullivan, Beard, and Bullock in 1976.[1] Since then numerous trials have demonstrated the efficacy of this mode of treatment and its advantages over epilation, electrolysis, radiotherapy, and surgery.[1-4]

Cryotherapy has not been used extensively in black patients because of the marked susceptibility of pigment cells to freezing and the subsequent problem of depigmentation.[5] Not only does this cause a cosmetic blemish but in patients living in hot climates there is the risk of actinic damage and its sequelae. This is unfortunate, as many of the people living in underprivileged parts of the world, with exposure to conditions such as trachoma, are dark skinned. The use of cryotherapy, which is easy to administer and not expensive compared with surgery, would offer many advantages. This paper describes a method of using cryotherapy to treat trichiasis in heavily pigmented lids, without using thermocouple control and with the avoidance of significant depigmentation. Many of the patients were treated on more than one occasion without significant adverse effects.

Material and methods

All procedures were performed in the minor outpatient theatre. Local anaesthesia was obtained with benoxinate 2% drops into the conjunctival sac and local infiltration of the lid with 2% lignocaine with adrenaline (1:100 000). A plastic spoon was positioned to protect the globe. The Collin cryoprobe attached to the Spembly-Amoils BMS-40 unit was used in this series with nitrous oxide as the cooling agent. Previous workers used a double freeze-thaw cycle whereby the probe was applied once to the conjunctival surface and once to the skin surface. This direct contact with skin incorporates a large area of skin within the iceball (Fig. 1A). We modified this technique by using a double freeze-thaw cycle applying the probe to the conjunctival surface and then to the lid margin (Fig. 1B). This prevents direct freezing of the skin and limits the area of skin incorporated into the iceball. The duration of application was 20 seconds to the lower lid and 25 seconds to the upper lid. It has been shown[2] that with this probe the desired temperature of −20°C can be consistently obtained at the level of the hair follicle if these time periods are used. A thermocouple was therefore not used to monitor the temperature. The lashes were not epilated. Chloromycetin ointment was applied and the eye padded for 24 hours. Patients were followed up at two weeks and again at six weeks after treatment. Thereafter they were seen when necessary or at three-monthly intervals. Any remaining lashes were epilated at the first post-treatment check, and, if aberrant lashes were found to have persisted or recurred at the second or subsequent visit, the patients were treated again in an identical fashion to that described above.

Results

Twenty-three patients and a total of 34 lids were treated. The causes of the trichiasis are given in Table 1. No pathological cause could be found in 27 lids. Many of these patients suffered from severe diffuse

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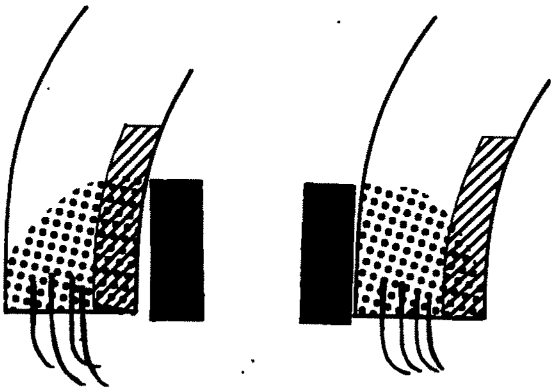

Fig. 1A *Usual method of applying the cryoprobe. A double freeze-thaw cycle is performed, the probe being applied in turn to the conjunctival and to the skin surfaces of the lid. During the latter application the iceball (stippled) involves a large area of skin.*

aberrant lashes, especially laterally, and this would appear to be a local genetic characteristic. The lower lid was affected in only four cases.

The median length of follow-up was 13 months, with a range of two to 26 months.

The results of treatment are shown in Table 2. Six patients (six lids) were excluded from the study because they were lost to follow-up. The criterion for successful treatment was elimination of aberrant lashes in the treated area with relief of symptoms. With repeated treatments the success rate was 82% (23 of 28 lids). Four patients showed some improvement after one application but were not treated further for various reasons. In one instance the machine was not working and the patient was subsequently lost to follow-up, two patients were referred for surgery because of concomitant dermatochalasis with entropion, and only one patient refused further treatment. One patient showed no improvement after a single treatment.

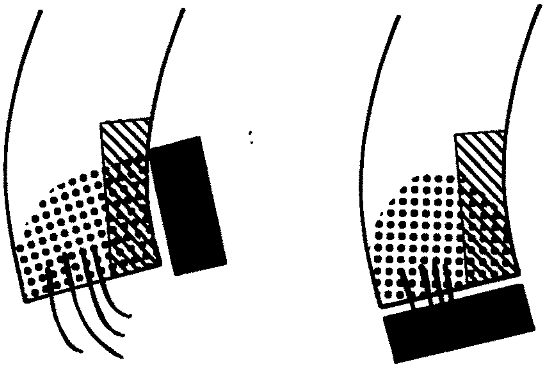

Fig. 1B *In our patients the cryoprobe was applied to the conjunctival surface and to the lid margin. The iceball (stippled) incorporates the lash follicles, but skin involved is kept to a minimum.*

The incidence of significant complications was low. Lid swelling occurred in all patients immediately after treatment but was usually of only moderate severity with mild discomfort. It settled within a week. Two patients developed lid notching after treatment; in both cases this followed a single application.

Lid depigmentation was graded into three groups: (O) no depigmentation or visible only with magnification; (I) Involving only the lid margin and not cosmetically objectionable (Fig. 2); (II) involving lid skin. Nineteen lids showed grade I depigmentation and one patient grade II depigmentation. The remaining eight lids had grade O depigmentation only.

Six patients subsequently developed trichiasis in untreated areas. In four cases this was adjacent to the treated area and in two cases in another lid.

Discussion

Pigment cells are extremely susceptible to freezing and can be destroyed at temperatures of −10°C.[6] Hair follicles are destroyed at temperatures of −20°C. It has been stated that depigmentation will always occur if trichiasis is effectively treated and that therefore this mode of treatment is not advised in black patients.[5] We believe that in reducing the degree of freezing of the lid skin by applying the probe as described above it is possible to reduce the amount of depigmentation to an acceptable level and still obtain satisfactory results.

This study demonstrates the successful use of cryotherapy to treat trichiasis without temperature monitoring by using a standardised probe for set time periods. This is important because thermocouples are expensive and being delicate instruments require

Tabe 1 *Causes of trichiasis*

Idiopathic	27
Trachoma	3
Trauma	3
Blepharitis	1

Table 2 *Results of treatment*

	No. of lids	
Lost to follow-up or deceased	6	
Success with 1st application	11	23
2nd application	9	
3rd application	3	
Improvement without eradication of aberrant lashes	4	
No improvement	1	

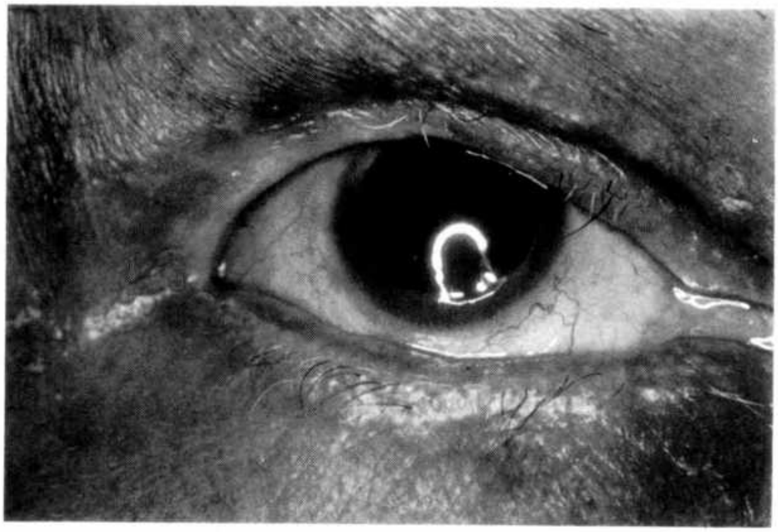

Fig. 2 *Grade I depigmentation. Only the lid margin skin is involved.*

much care in their use. The absolute necessity of using them would restrict the scope of cryotherapy for trichiasis greatly. It is also an advantage to be able to use a nitrous oxide probe, as this type of machine is now widely available and is more convenient than other methods of cooling. It should be noted that the retinal cryoprobe does not have a sufficiently high cooling rate to provide fast enough freezing within the lid tissue. Other workers[6 7] using this method, with or without temperature monitoring, have shown a lower success rate.

We have used cryotherapy on as many as three occasions to the same area of the lid without an increase of complications. Wood and Anderson,[8] who reported a high incidence of complications, also treated lids on up to four occasions but did not relate the complication rate to the number of applications. The low number of complications in our study may be due to the method used or possibly to the initial absence of associated conjunctival disease in our patients.

This method of treatment was very acceptable to our group, and only one patient refused a second application. Treatment was given as an outpatient procedure on the day that the patient was seen in clinic. As well as being convenient to patients, expensive hospital admissions and surgery can be avoided.

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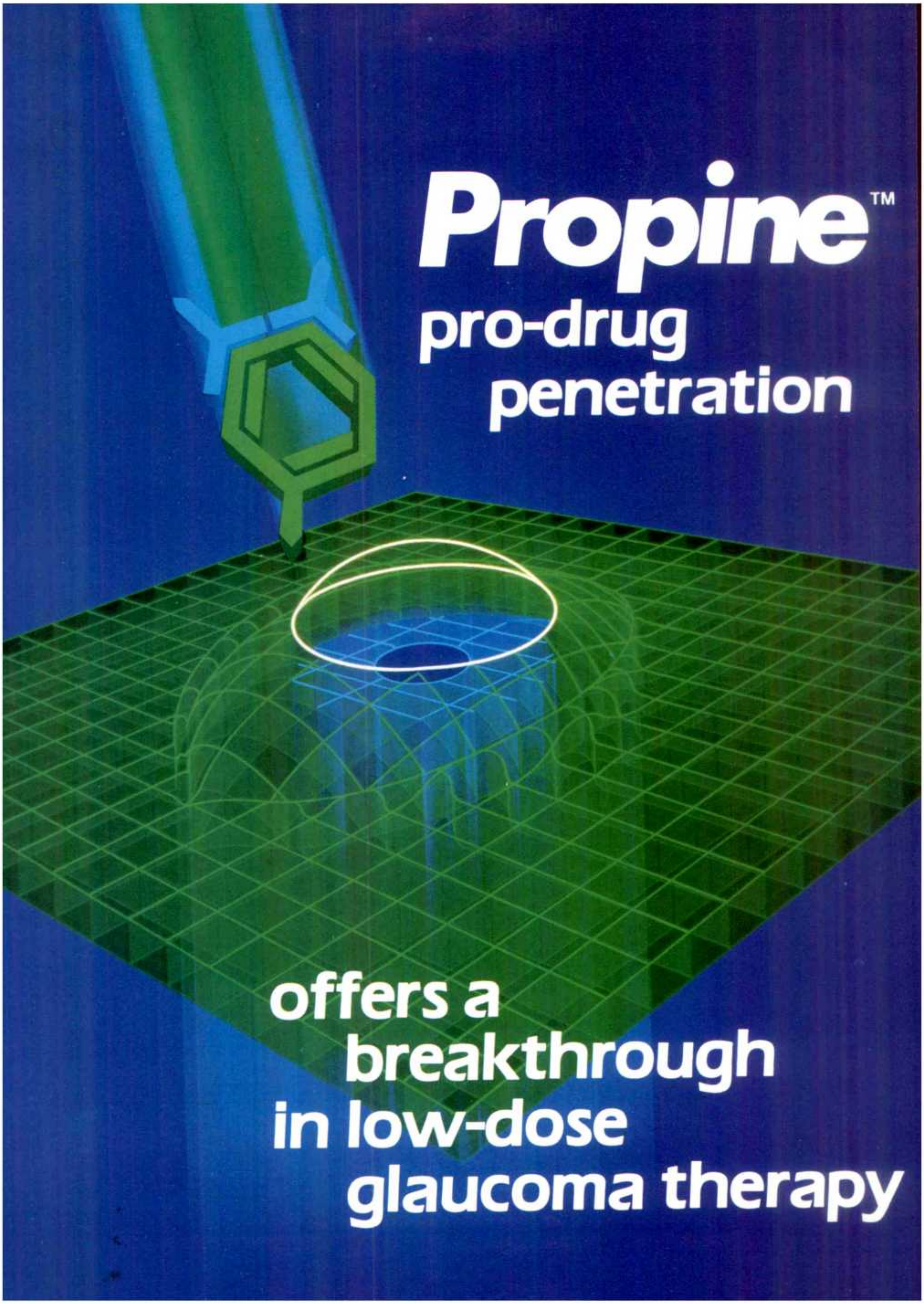
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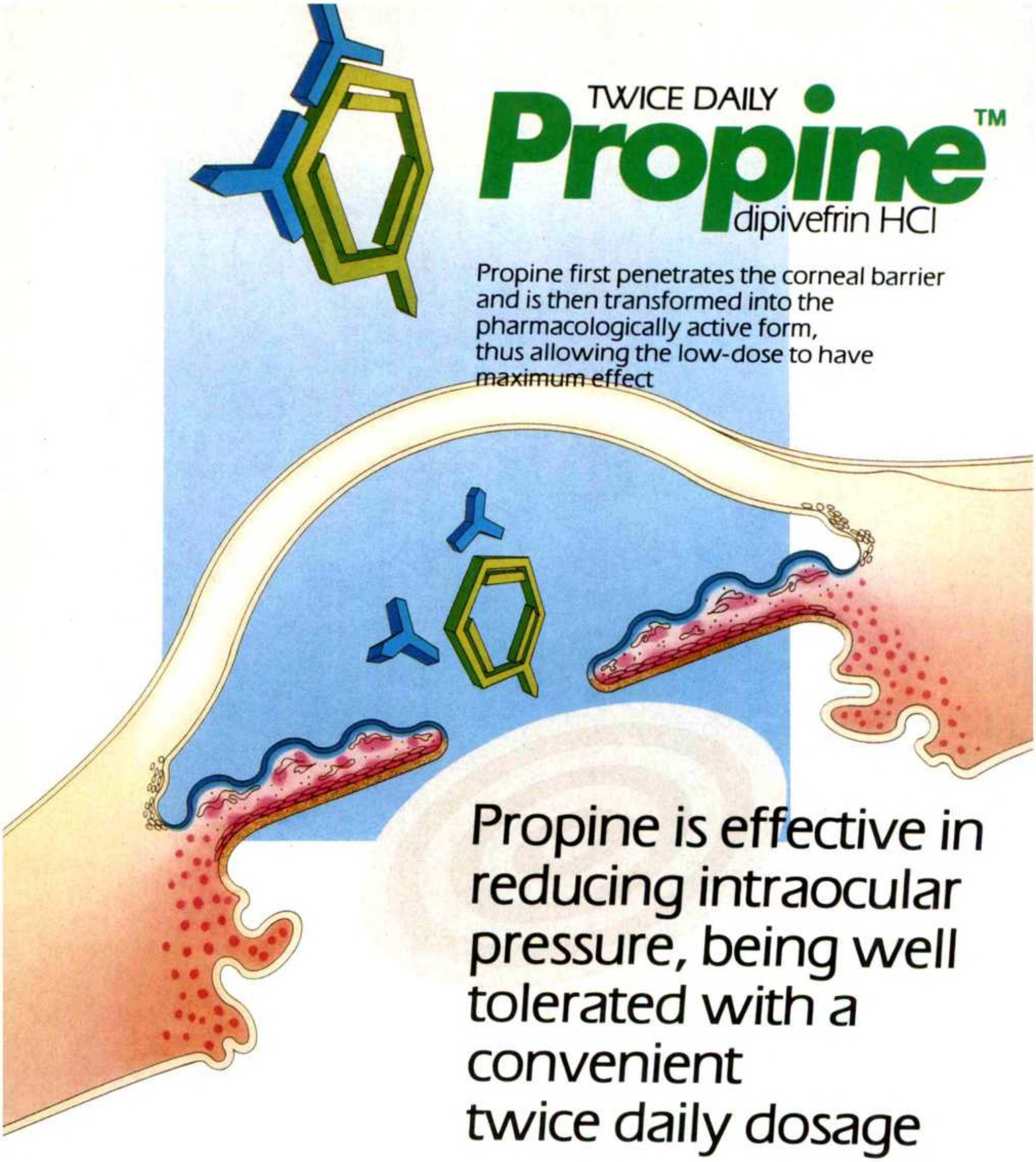

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Autosomal dominant juvenile onset glaucoma affecting six generations in an Edinburgh family

SIR, Crombie and Cullen reported a five generation pedigree of autosomal dominant juvenile onset glaucoma in 1964.[1] We have now examined the two members of the sixth generation, both of whom have developed juvenile onset glaucoma, associated with abnormal drainage angle appearance. The two cases are the daughters of case V1 (as described previously[1]).

Case 1 presented to the Eye Department at age 21 years, complaining of coloured haloes around lights and contact lens intolerance. Intraocular pressure was 28 mmHg in the right eye and 42 mmHg in the left. Cup:disc ratios were 0·5 in the right eye, 0·6 in the left. Visual fields were full. Gonioscopy revealed open drainage angles with fine white lacey tissue and fine blood vessels. She had been examined at age 7 years because of the known family history of glaucoma. At that time intraocular pressures had been 14 mmHg in each eye, with normal optic discs.

Case 2 was examined at age 17 years, following the finding of glaucoma in her sister. She was asymptomatic. Intraocular pressure was 34 mmHg in each eye, with a cup:disc ratio of 0·9 in the right eye and 0·8 in the left. Visual fields were full. Gonioscopy revealed open angles, with white lacey tissue and large blood vessels at the level of the trabecular meshwork in many areas. She had been examined at age 4 years, when the corneal diameters and optic disc appearances were normal.

The sixth generation of this family, along with member V2, as previously described,[1] have been clearly demonstrated to have autosomal dominant juvenile onset glaucoma, with abnormal tissue in the drainage angles. Although the classification of juvenile onset glaucoma remains in dispute,[2,3] the combination of features in this family justifies acceptance as a distinct disease entity.

Princess Alexandra Eye Pavilion, B W FLECK
Chalmers Street, J F CULLEN
Edinburgh EH3 9HA

References

1 Crombie AL, Cullen JF. Hereditary glaucoma. Occurrence in five generations of an Edinburgh family. *Br J Ophthalmol* 1964; **48**: 143–7.

2 Leydhecker W. Simple glaucoma before the age of 30 years. *Ophthalmologica* 1979; **178**: 32–6.

3 Goldwyn R, Waltman SR, Becker B. Primary open angle glaucoma in adolescents and young adults. *Arch Ophthalmol* 1970; **84**: 579–82.

Book reviews

Ophthalmology Annual: Nineteen eighty-six. Edited by ROBERT D. REINECKE.. Pp. 264. £64·15. Appleton-Century-Crofts: Norwalk, Connecticut. 1986.

1985 obviously was not a year for major ophthalmological advances to judge by the contents of this book. It contains reviews of 13 assorted topics which vary in their quality, length, and content. They are written by separate authors and cover subjects which vary from chalazions and their treatment (nothing new here) to a review of cystoid macular oedema, retrolental fibroplasia, two chapters on intraocular lenses, thyroid eye disease, and others. No present ophthalmic publication is complete without a section on radial keratometry and this book is no exception, with the author concluding after quite a good chapter that RK will achieve greater acceptance in time. My feeling is that this slim volume may provide bedtime browsing material, but few people will miss anything if they do not read it.

D J SPALTON

Infectious Diseases of the Eye. By GILBERT SMOLIN, KHALID TABBARA, AND JOHN WHITCHER.. Pp. 182. £32·00. Williams and Wilkins: London. 1984.

This book, the latest and one of the better volumes in a series of handbooks in ophthalmology, is intended to provide the practising ophthalmologist with a concise and up-to-date account of infectious disorders of the eye and adnexae. The text is arranged on anatomical grounds in seven chapters with an introductory section largely given over to a pragmatic description of laboratory diagnosis. The format of most chapters comprises a brief description of the relevant anatomy, the symptomatology and manifestations of infectious disorders, and specific isolation techniques. Epidemiological considerations, causative agents, and the rationale and principles of prophylaxis and therapy are all dealt with in a reasonably comprehensive manner in most sections. The chapters devoted to microbial keratitis and endophthalmitis are particularly informative and well balanced, with sufficient attention paid to controversial issues, for example the role of vitrectomy in endophthalmitis. Throughout this volume the text is particularly well complemented by carefully selected black-and-white illustrations of excellent clarity and detail. My only major criticism is that in a number of sections the bibliography contains a disappointing number of references to the literature of the past five years which in some respects detracts from the overall value of the book.

Broadly speaking this is a well written treatise on infectious ocular disease which is both enjoyable to read and readily assimilated. The authors have achieved their stated intention to provide concise and comprehensive coverage of clinical ocular microbiology, and as such it is a welcome addition to the current ophthalmic literature.

R J COOLING

Notes

BCLA scientific meetings

The British Contact Lens Association will hold scientific meetings at the Royal Society of Medicine, 1830 for 1900 h, as follows: 9 September (presidential address, Mr M Jaggs), 27 October (Dallos Award lecture, Mr J Molinari), 26 January 1987, and 2 April 1987 (titles to be announced later).

Hellenic congress

The 20th Annual Hellenic Ophthalmological Congress will be held on Rhodes on 28-30 May 1987, with simultaneous translation in Greek and English. Details from the Secretariat, 20th Panhellenic Ophthalmological Congress, 10 Loukianou Street, 106 75 Athens, Greece.

Ophthalmic registered nurses

The American Society of Ophthalmic Registered Nurses will hold its 10th Annual Meeting, Insight into eyesight: 'In Pursuit of Excellence,' on 10-12 November 1986 at the Marriott Hotel, New Orleans, Louisiana. Information from Sue Brown, Administrator, ASORN, Inc., PO Box 3030, San Francisco, California 94119, USA.

Pakistan congress

The All Pakistan 10th Annual Ophthalmic Congress will be held on 26-28 February 1987 at the twin cities of Rawalpindi-Islamabad. There will be special sessions on external diseases of the eye and on diagnostic and therapeutic implications of fundus fluorescein angiography. Details from Congress Secretariat, Rawalpindi General Hospital, Rawalpindi, Pakistan.

Singapore meeting

The dates for the International Cataract, Implant, and Microsurgical Meeting which will be held in Singapore at the Shangri-La Hotel, are now changed to 13–15 June 1987. This is a joint meeting of the International Intraocular Implant Club and the Asia-Pacific Intraocular Implant Association. Further information from Dr Arthur S M Lim, 3 Mt Elizabeth 0605-0608, Mt Elizabeth Medical Centre, Singapore 0922.

Neuro-ophthalmology

An update in neuro-ophthalmology in honour of William F Hoyt, MD, will be held by the University of California School of Medicine at San Francisco on 11–12 December 1986 at Hyatt on Union Square, San Francisco, California. Details from the University of California, San Francisco, California 94143, USA.

Master's degree programme in public health ophthalmology

A special master's degree programme in preventive ophthalmology will be offered during 1987–8 by the Johns Hopkins Medical Institutions under the auspices of its International Center for Epidemiologic and Preventive Ophthalmology, a World Health Organisation Collaborating Center. The programme is designed for individuals interested in initiating, developing, and providing leadership to national or regional blindness prevention activities and in conducting serious clinical epidemiologic research. Ten to 15 places are available for participants from developing and developed countries. For further information write to Program Coordinator, Preventive Ophthalmology Program, ICEPO, Wilmer Institute, Room 120, Johns Hopkins Hospital, 600 N Wolfe Street, Baltimore, MD 21205, USA.

Symposium in China

A clinical ophthalmological symposium will be held on 15–16 November 1986 at the Bai Yun Hotel, Huanshi Dong Lu, Guangzhou, China. Details from Patrick C Ho, MD, Eye Unit, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong, or Lezheng Wu, MD, Zhongshan Ophthalmic Centre, Sun Yat-sen University of Medical Sciences, Guangzhou, China.

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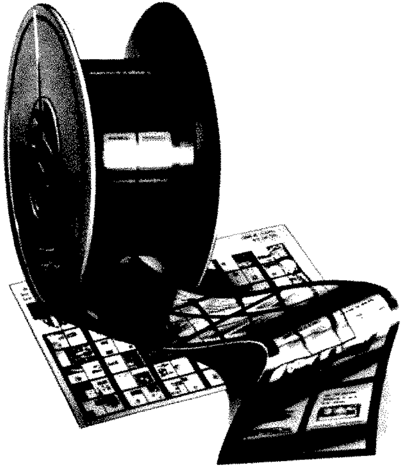

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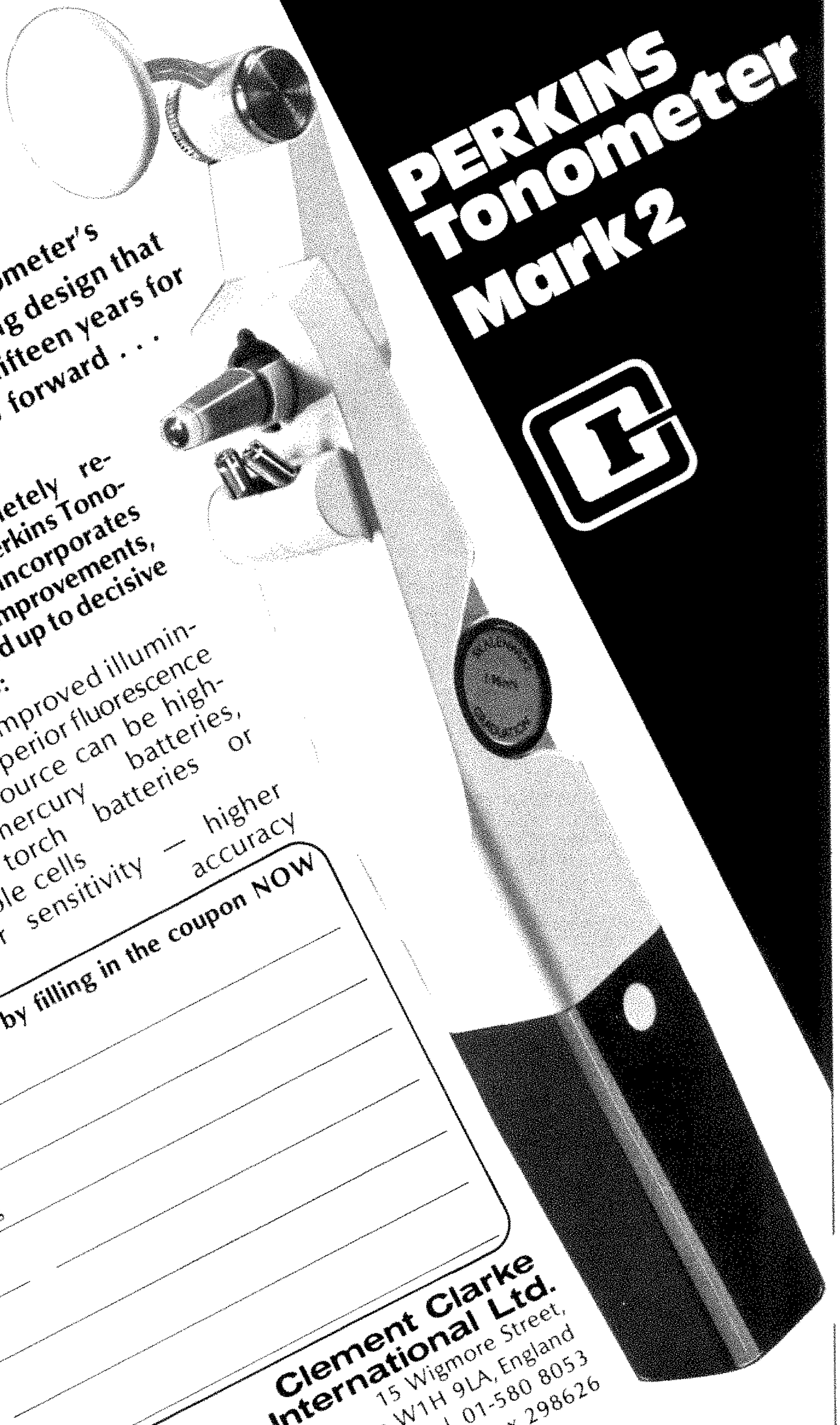

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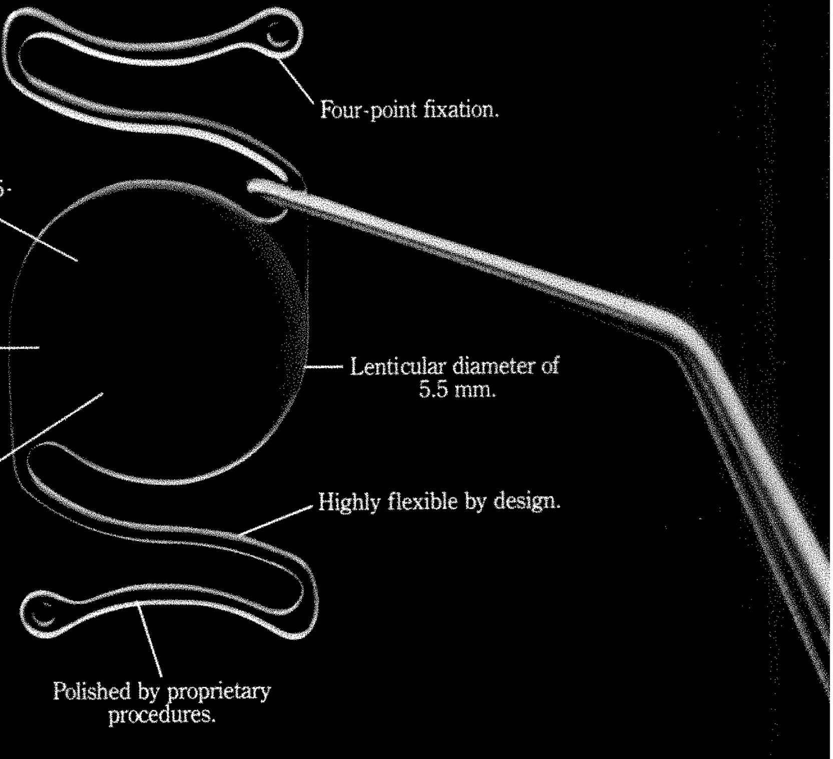
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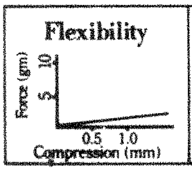

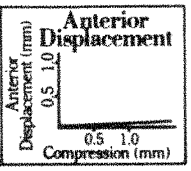

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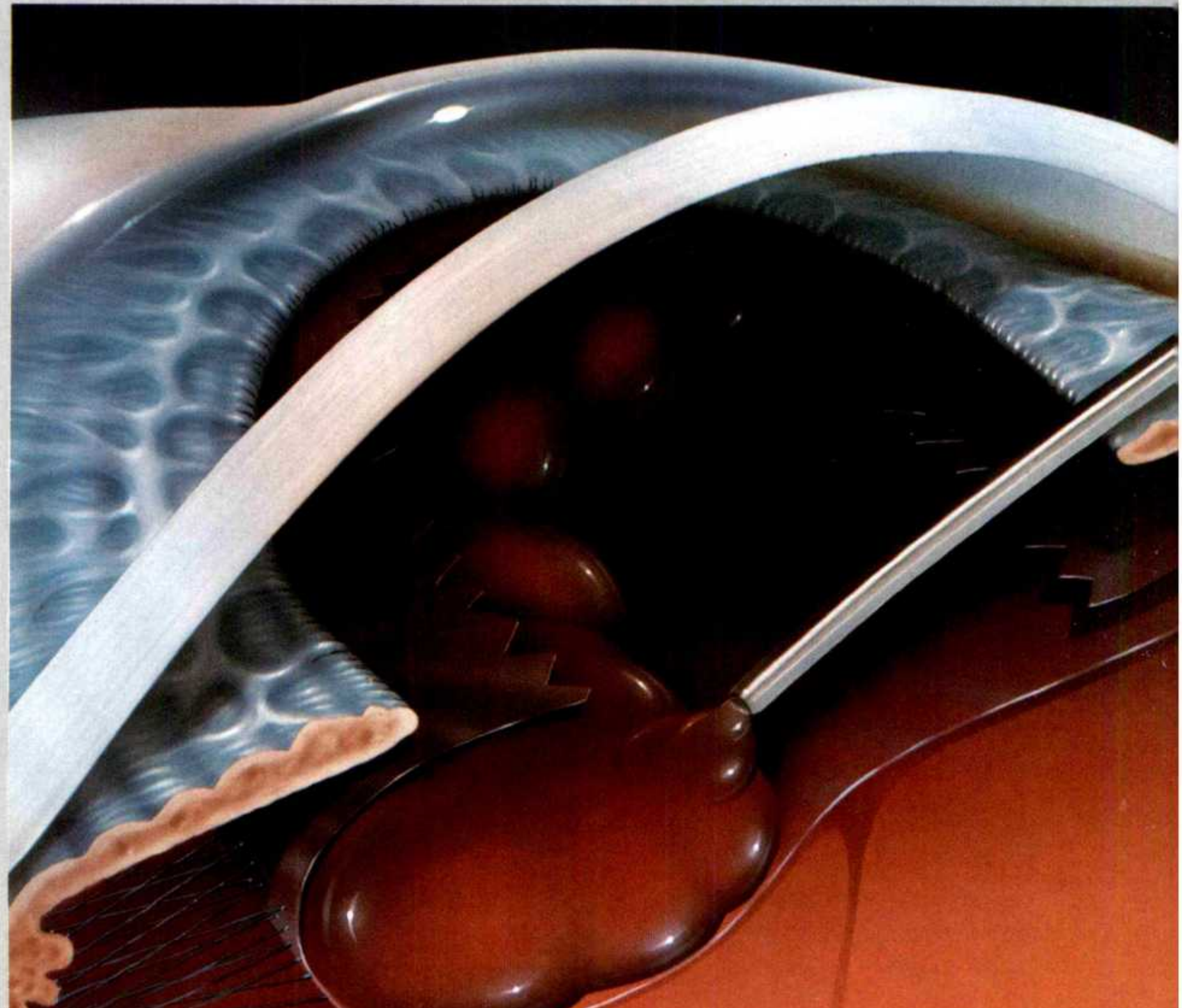

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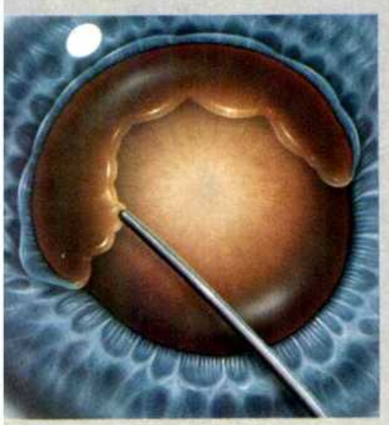

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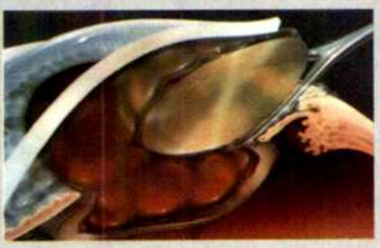

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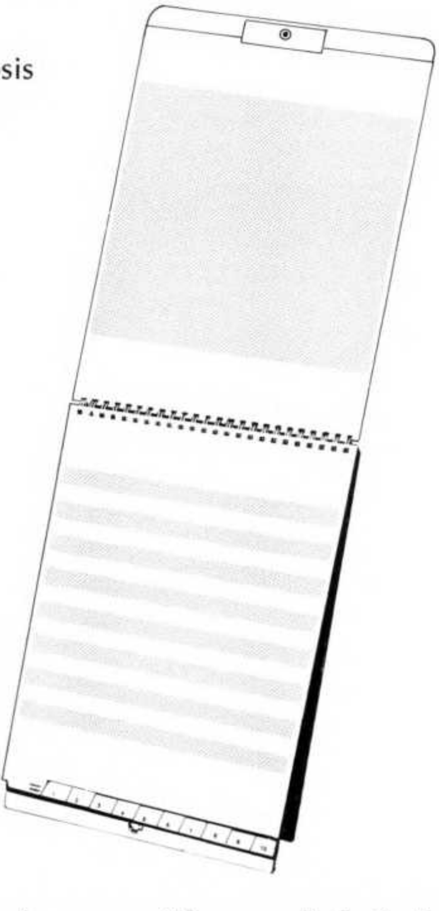

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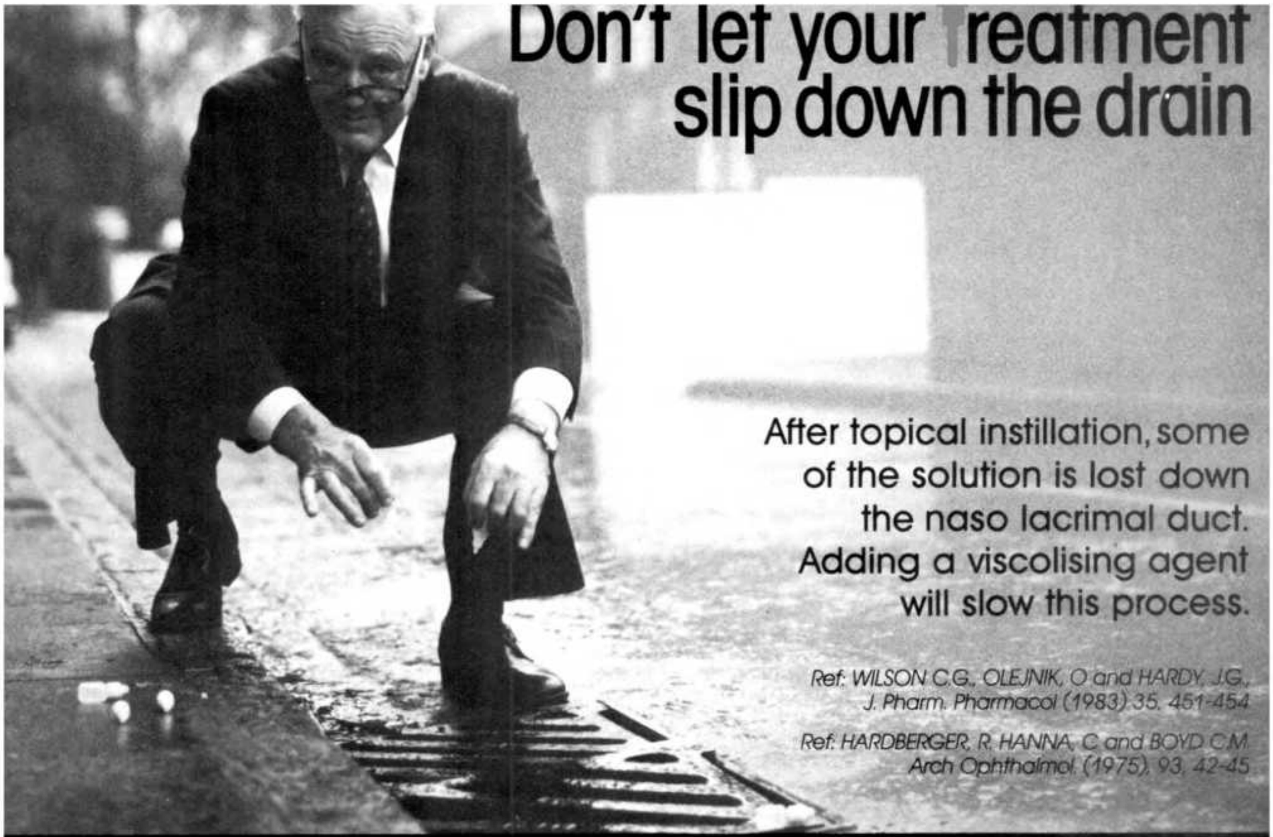

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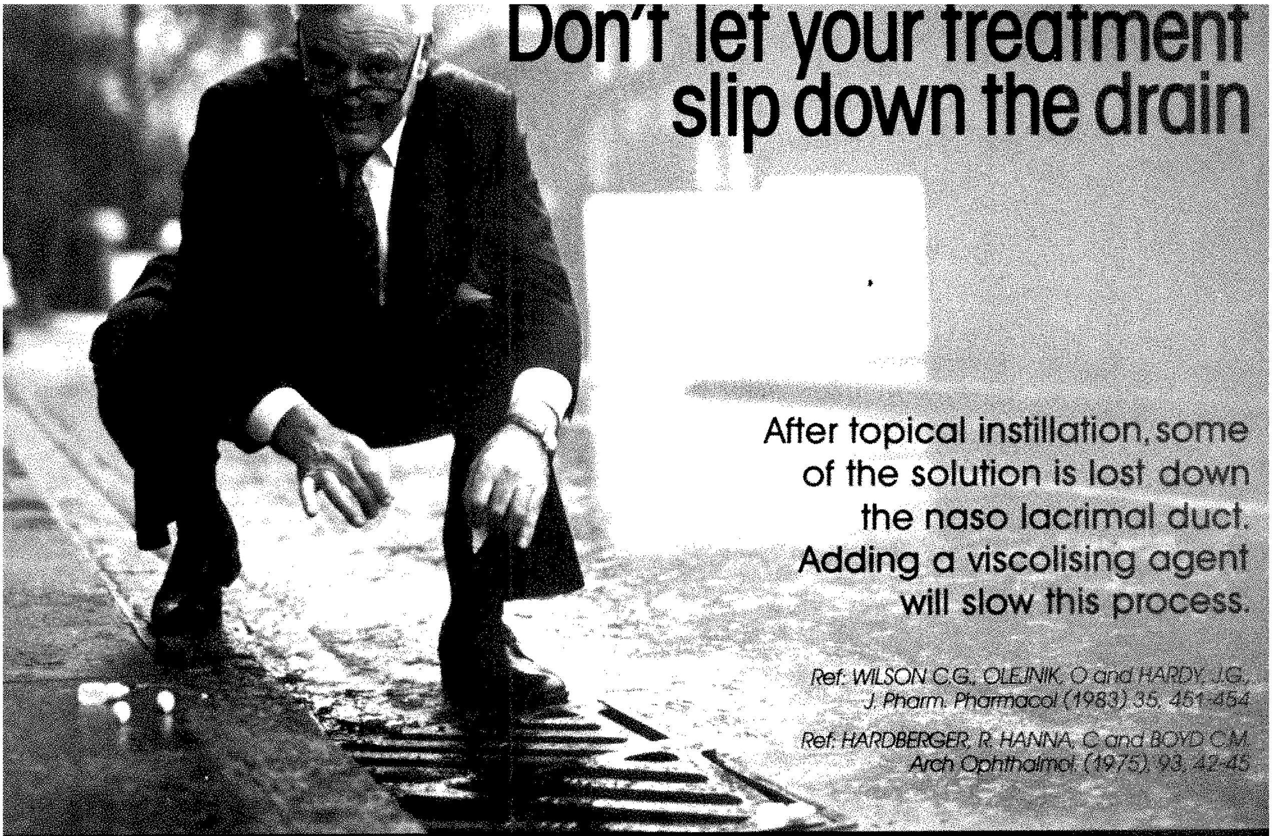

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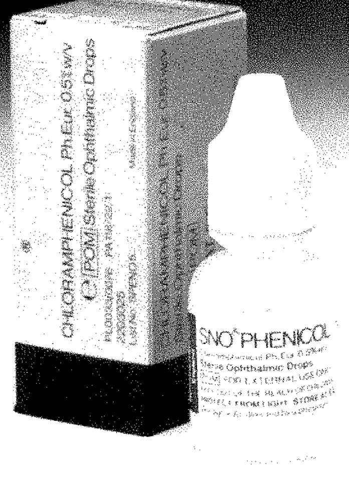
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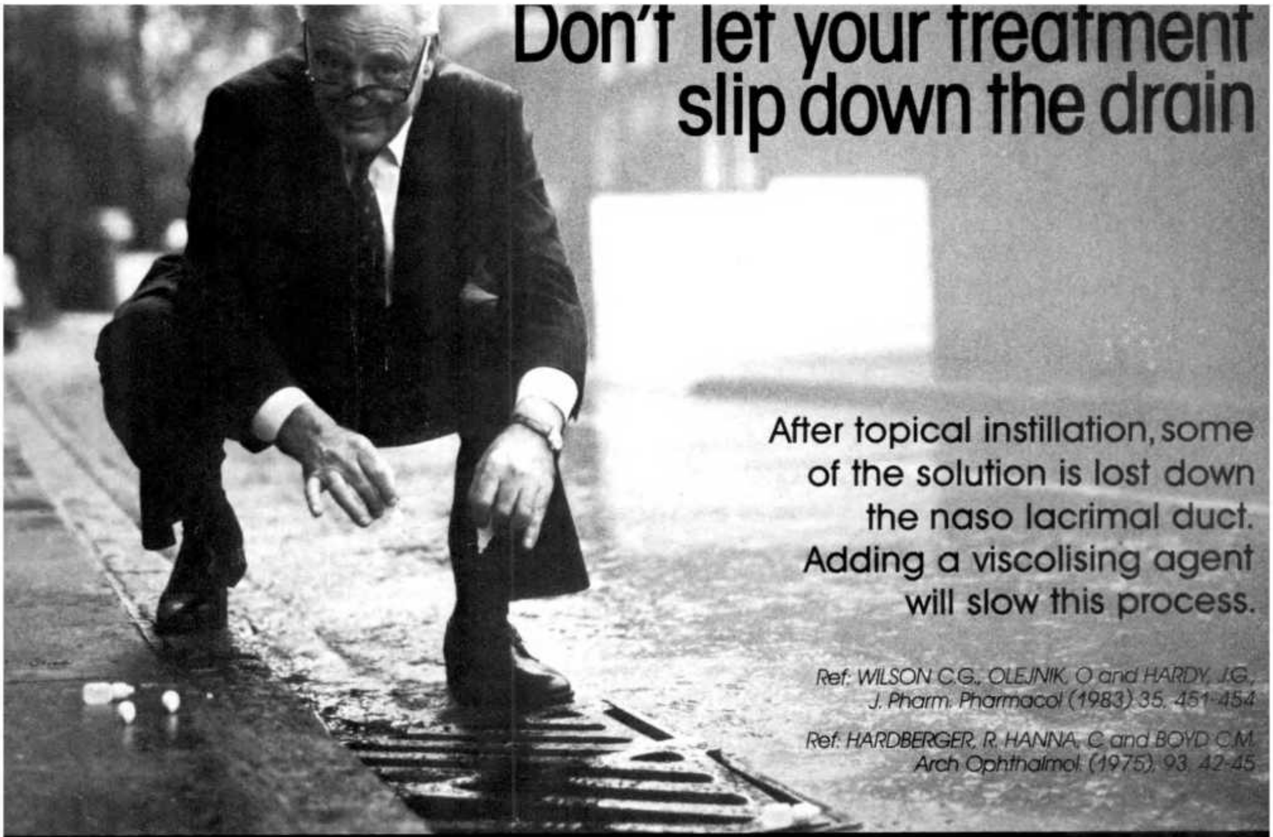

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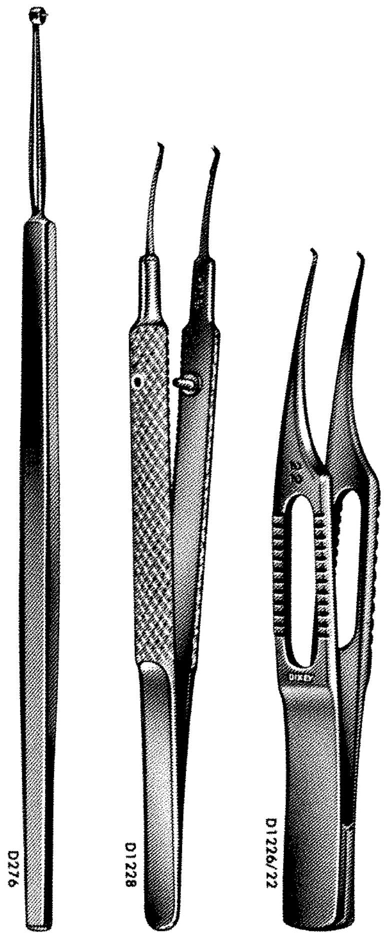

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1. Hopkins, G.A., *Am J Optom Physiol Opt*, 1985, **62,** (2), 132-141. 2. Demmler, N., *Der Augenspiegel*, 1980, 238-243.
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British Journal of Ophthalmology, 1986, **70**, 717

Editorial: Random dot stereoscopic slides

Fascinating issues are raised by the paper by Archer, Miller, Helveston, and Ellis in this number of the *BJO*. I have always wondered how genuine the oft-quoted mechanisms concerned with binocular and stereoscopic vision really are. Disparate images, Panum's area, diplopia avoidance, all have a somewhat unsatisfying and rather negative quality as explanations for the brilliant mechanism of binocular stereoscopic vision. The whole business of using both eyes together is mysterious: almost everything is "diplopic" around us except our "object of regard," and yet we do not seem to notice it. Admittedly we can make it rather obvious, for example by holding up a pencil while looking at the television, when the pencil will appear double. Interestingly enough, if the pencil is fixated the "doubleness" of the picture on the television is not nearly so obvious unless captions appear. Thus there seem to be two sorts of physiological diplopia—the usual "unnoticed" type and the more contrived "noticed" type, where a solitary object is deliberately singled out for attention but not fixation.

Since therefore that we accept so much diplopia in everyday life with equanimity, it is perhaps a little surprising that when "true" diplopia occurs it is so catastrophically different from the so-called "physiological" variety. The difference must surely lie in the interpretative interaction between eye and brain, in which the search for meaning, for evidence of reality, for correspondence with other experiences, for a good fit with the previously perceived facts of life, is relentlessly pursued by our senses and our brain acting in concert. Thus our continual visual "surveillance" of our environment seems to involve a series of extremely rapidly repeated judgments.

We tend to reject the impossible (two different objects in the same place at the same time, so-called confusion), the apparently absurd (true diplopia), or the chaotic (the random dots) and to hold on for as long as possible to any image which appears to have order and meaning. However, since diplopia is so commonly seen as a physiological phenomenon, as mentioned above, it is not altogether surprising that its avoidance is not necessarily central to the maintenance of fusion, as Archer and colleagues have now shown.

I have always thought of stereoscopic vision as a form of rationalisation. First we look at the cube slightly from the right, then slightly from the left, and after a bit (? a few milliseconds) the penny drops that it *is* a cube, in other words it is stereoscopic. Actually, you can do this almost as well with one eye if you move your head from side to side. You can even do it to some extent when viewing an optic disc with a direct ophthalmoscope and can immediately obtain a weak stereoscopic effect. Perhaps "monocular weak stereopsis" would be a better term that the somewhat infelicitous mouthful "parallax." My dictionary defines it as "apparent displacement of an object, caused by actual change of the point of observation." However, this definition would apply only to a theoretical point object. A lot more happens to a real object. For example, the side of our previously mentioned cube actually changes shape or, given a big swing of the head, may even disappear completely.

Thus the somewhat unsatisfactory explanations about stereopsis depending on "disparate images" and fusional reserve being used to "avoid diplopia" have hitherto seemed a bit thin, so it is most exciting to get some new information from Archer and his colleagues strengthening the "order out of chaos" philosophy.

RJHS

British Journal of Ophthalmology, 1986, **70**, 718–723

Vergence amplitudes with random-dot stereograms*

STEVEN M ARCHER, KATHLEEN K MILLER, EUGENE M HELVESTON, AND FORREST D ELLIS

From the Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana, USA.

SUMMARY Random-dot stereograms were found to be capable of producing fusional vergence amplitudes in the absence of monocular contours. These vergence amplitudes are not an artefact of monocular contours provided by the target borders or test instrument and are comparable in range to vergence amplitudes measured clinically with second degree fusion targets in an amblyoscope. We conclude that diplopia of monocularly recognisable contours is not necessary for producing fusional vergence amplitudes.

Fusional vergence amplitudes reflect the ability of the oculomotor system to maintain sensory fusion in spite of varying vergence requirements. Traditionally this has been regarded as a diplopia avoidance mechanism. However, Hyson *et al.*[1] have recorded vergence responses to divergent misalignment of random-dot stereogram targets which do not feature monocularly recognisable contours which could give rise to diplopia.[2] The purpose of this paper is to show that these vergence amplitudes are not artefacts due to target borders or an optokinetic response. We also compare these vergence amplitudes with those obtained clinically with second degree fusion targets in an amblyoscope.

Subjects and methods

EXPERIMENT 1

The ability of random-dot targets to produce vergence amplitudes at the amblyoscope was tested for five normal subjects. The random-dot targets included a stereogram with nonius lines[3] (Fig. 1), a positive/negative stereogram[4] with nonius lines (Fig. 2), and a stereogram with ragged edges (Fig. 3). One

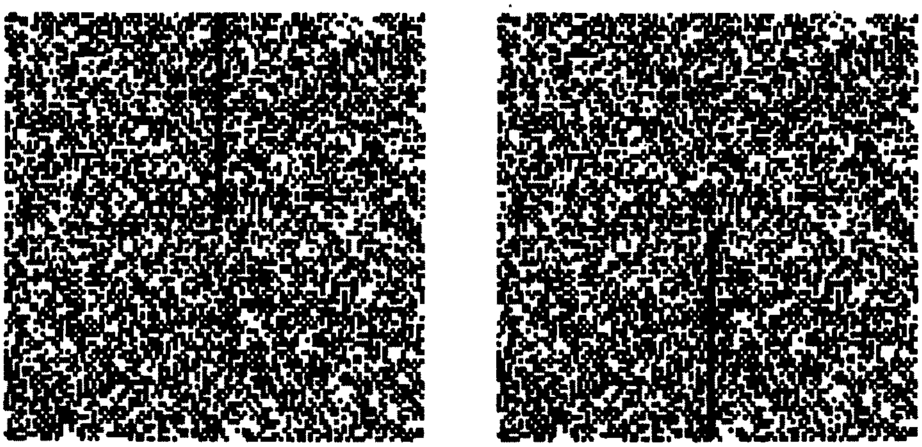

Fig. 1 *Random-dot stereogram with nonius lines added (narrower and in red on actual targets used). Images subtended 18° by 18° with 6·5° by 7·5° central rectangle in 40′ crossed disparity. Exchange right and left images for viewing in a mirror haploscope.*

---

*Read in part before the Association for Research in Vision and Ophthalmology, Sarasota, Florida, 10 May 1985.

Correspondence to Steven M Archer, MD, Department of Ophthalmology, IU Medical Center, Indiana Lions Eye Care Center, 702 Rotary Circle, Indianapolis, IN 46223, USA.

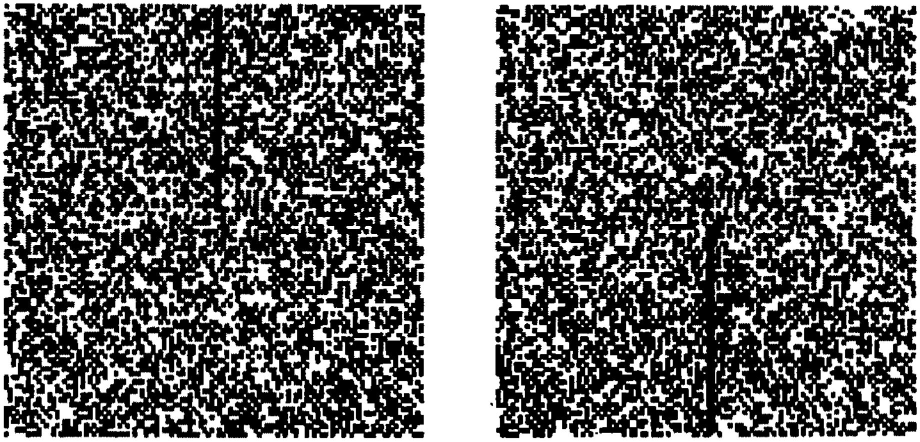

Fig. 2 *Positive and negative image stereogram with nonius lines. Identical to Fig. 1 except that all points in left image have been complemented (after Julesz[4]).*

subject had eye movements recorded electro-oculographically during amblyoscope testing. The details of the vergence testing are described in experiment 2. These five subjects were also tested with a dynamic random-dot stereogram.[5] The stereo image pair was displayed on two television monitors which were mounted on the arms of a Wottring Troposcope.

EXPERIMENT 2

The vergence amplitudes of 16 normal subjects were tested with conventional amblyoscope fusion targets and random-dot stereogram targets (Fig. 4). Subjects were excluded from the study if they showed any heterotropia, a heterophoria in excess of 6 prism dioptres, or any abnormality of ductions or versions.

Vergence amplitudes were measured with an amblyoscope (American Optical Wottring Troposcope). No attempt was made to control accommodation. With the conventional second degree fusion targets the divergence break point, divergence recovery point, convergence break point, and convergence recovery point were measured by slowly and symmetrically diverging and converging the haploscope arms. The random-dot stereogram slides were then placed in the haploscope, the subjects were allowed time to obtain stereopsis while viewing at their subjective angle, and the same sequence of measurements was repeated. Reported loss and recovery of the stereoscopic form were taken as the break and recovery points. Informed consent was obtained from all subjects.

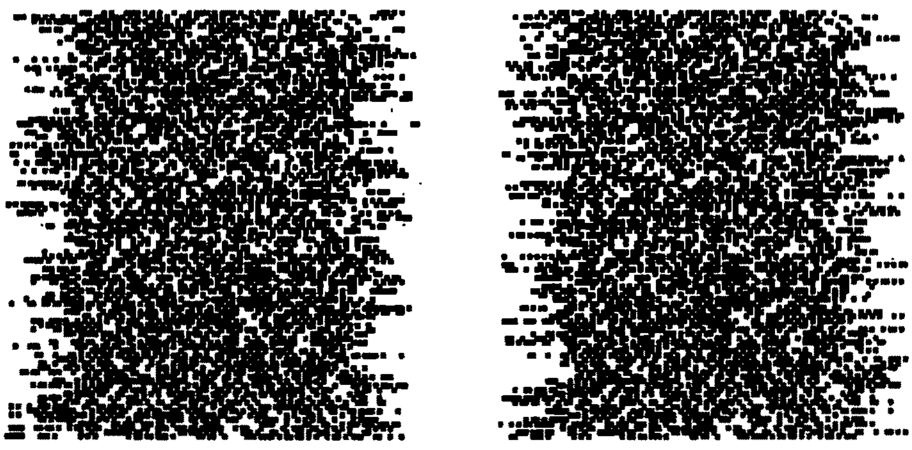

Fig. 3 *Stereogram with ragged edges. Identical to Fig. 1 (without nonius lines) except that all vertical borders have been randomly indented from 1 to 20 dots.*

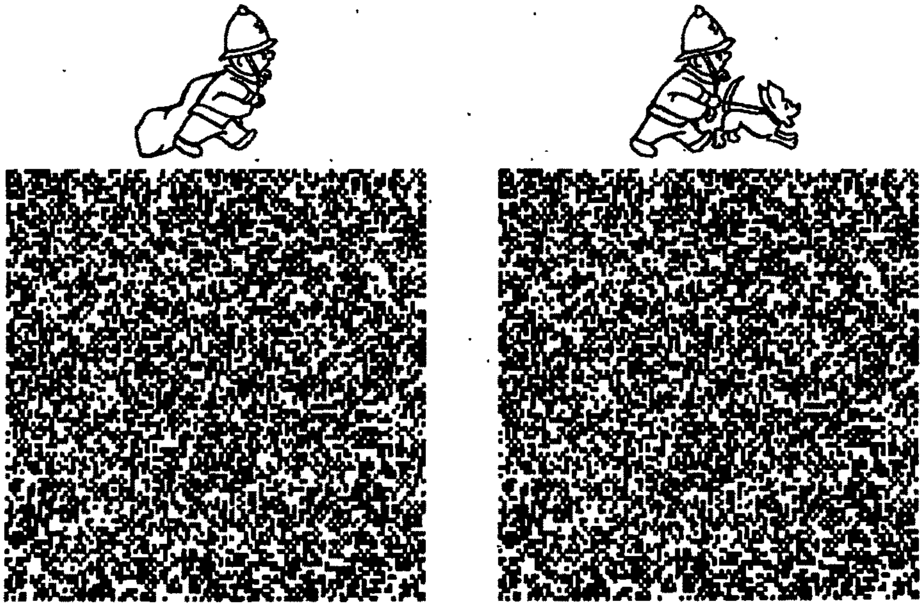

Fig. 4 *Amblyoscope target pairs. Top, second degree fusion targets subtending 7·25° by 5·2°. Bottom, random-dot stereogram targets subtending 15° by 15°. A 9° by 9° block letter T is portrayed in 35′ crossed disparity (after Julesz[2]).*

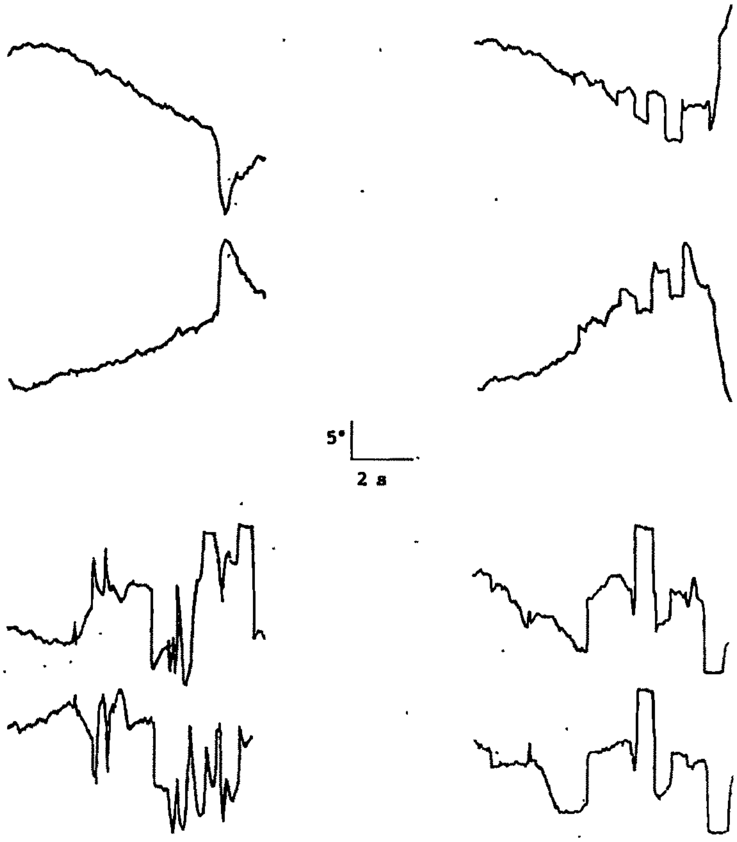

Fig. 5 *Electro-oculographic records of convergence testing. Top tracing is right eye, upward deflection is right. Targets tested were conventional fusion target (top left), ragged-edge stereogram (top right), positive/negative stereogram with nonius lines (bottom left), positive/negative stereogram without nonius lines (bottom right).*

Results.

All five subjects gave the same results in experiment 1 and will be reported as a group. In brief, vergence amplitudes comparable to those with conventional second degree fusion targets were elicited by the stereogram with nonius lines, the stereogram with ragged edges, and the dynamic random-dot stereogram. Only a minimal vergence response could be elicited with the positive/negative stereogram.

In the first stereogram nonius lines served as non-fusible indicators of ocular alignment in addition to the report of fusion. When initially fused at the subjective angle the nonius lines showed an uncrossed displacement of four picture elements, which was equal to the number of dots by which the central target area had been shifted in this particular target. That is, for a stereogram with crossed target disparity in which the target appears in front of the background, the vergence position assumed was such that the dots in the target region actually had zero disparity while the background dots were left in a state of uncrossed disparity. (However, when the target region was portrayed in uncrossed disparity, only one subject reported any displacement of the nonius lines and then only with conscious effort after viewing the target for considerable time.) This displacement of the nonius lines was stable and maintained over the entire range of vergence tested except just prior to the break points. There was a shift of the nonius lines while the arms of the haploscope were in motion from one vergence angle to another, but the same stable nonius line displacement was promptly restored when the movement stopped.

It was not possible to appreciate the embedded stereogram in the positive/negative random-dot target pair, so the nonius lines served as the only indicator of whether or not a correct vergence position was being maintained. The nonius lines were aligned when the targets were presented at the subjective angle. When the amblyoscope arms were moved within a small range round this position, it was possible to keep the lines close to each other, but this was unstable and required some effort. Alignment was not possible outside this small range.

Eye movements were recorded electro-oculographically in one subject (Fig. 5). They were consistent with the eye movements inferred from the previous subjective responses. Convergence was recorded with the conventional second degree fusion targets and the ragged-edge stereogram. Minimal convergence was seen with the positive/negative random-dot targets with nonius lines. There was frequently no response at all to the positive/negative targets without nonius lines, but when a response was present it was an ill-defined version movement (Fig. 5, bottom right). These latter two findings indicate that the minimal amplitudes observed subjectively with the positive/negative target with nonius lines were probably due solely to the nonius lines.

Quantitative results obtained from 16 normal subjects comparing conventional second degree fusion targets with random-dot stereogram (Fig. 4) were as follows: the average divergence amplitude was 9 prism dioptres (5°) for both second degree fusion targets and random-dot targets with standard deviations of 2 and 1 prism dioptres respectively. The average convergence amplitude was 22 prism dioptres (12·4°) for both second degree fusion targets and random-dot targets with standard deviations of 13 and 11 prism dioptres respectively. The distribution of individual differences in performance between random-dot and second degree fusion targets (Fig. 6) does not indicate any systematic difference between the two target types.

The difference between maintaining fusion and

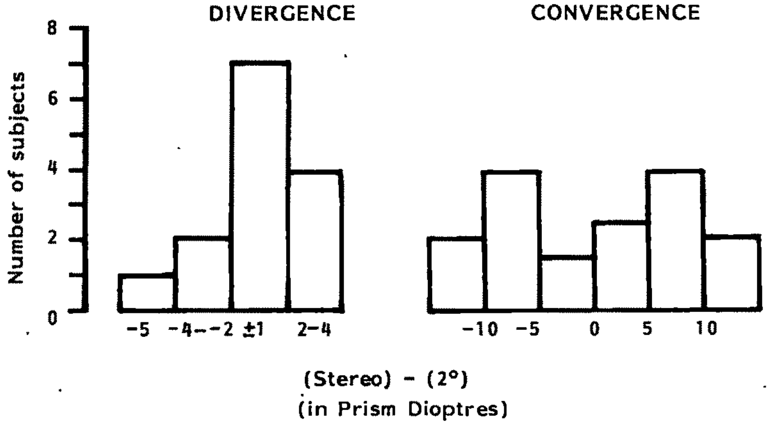

Fig. 6 *Histograms of vergence amplitude differences with second degree and random-dot targets. Absolute vergence amplitude with stereogram minus amplitude with second degree targets for divergence (left) and convergence (right).*

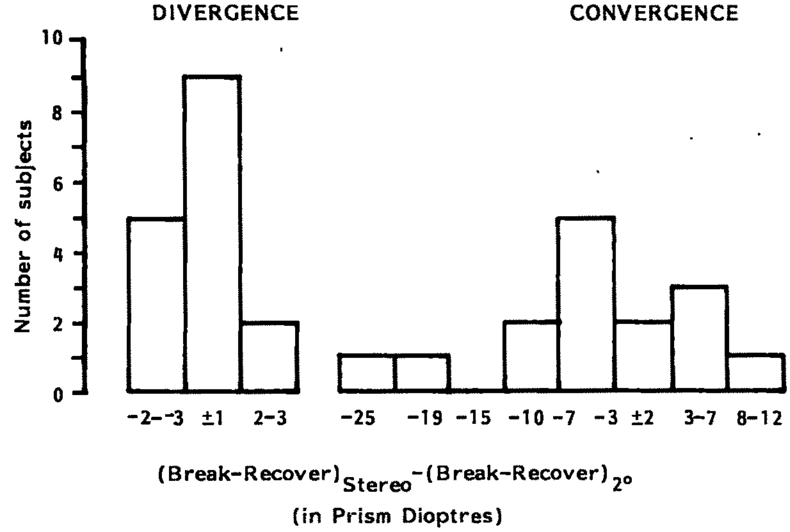

Fig. 7 *Histograms of hysteresis differences with second degree and random-dot targets. Difference between break and recovery with stereogram minus difference between break and recovery with second degree fusion targets for divergence (left) and convergence (right).*

acquiring fusion was demonstrated during vergence amplitude testing by the difference between the break and recovery points. Individual differences in this hysteresis with random-dot and conventional second degree fusion targets are shown in Fig. 7. Two subjects had essentially no recovery during convergence testing with the random-dot targets. The two target types gave similar hysteresis characteristics for the remainder of the subjects. The 95% confidence intervals (Student's *t* test) for the differences in hysteresis between stereogram and conventional fusion targets were −0·5±1·0 and −3·0±5·5 prism dioptres for divergence and convergence respectively. This reflects a slight skew toward earlier recovery with conventional fusion targets, but it is not significant statistically.

Discussion

Fusional vergence amplitudes are the result of eye movements directed towards maintaining sensory fusion. This is sometimes regarded as a diplopia avoidance mechanism. The stimulus for vergence amplitudes is generally described as disparity between a contour in the image from one eye and a similar contour in the image from the other eye (potentially diplopic contours). These experiments appear to show that disparity detected by global processes is also capable of producing a motor response resulting in vergence amplitudes. However, care must be taken to rule out other possible explanations, since global disparity detection is widely recognised as being associated only with the sensory process of stereopsis (as demonstrated with random-dot stereograms).

One possible objection might be that all contours have not been eliminated. The borders of the dot patterns or the instrument tube edges might produce the observed vergence amplitudes. However, normal vergence amplitudes with the ragged-edge stereogram and the lack of real vergence amplitudes in the control case of the positive/negative stereogram would indicate that these residual contours are not necessary, nor are they adequate for producing vergence amplitudes.

An alternative explanation is that some sort of optokinetic vergence response to the shifting fields of dots produced the observed vergence amplitudes. This could not be the case with the dynamic random-dot stereogram in which the entire pattern is replaced every 1/60 second and no dot is on the screen long enough for its movement to be detected.

If diplopia of extended contours is not the motivation for the observed vergence with random-dot targets, is it possible that diplopia on a dot-by-dot basis serves this function? This explanation does not seem adequate. For diplopia to occur, pairs of dots (one from each retinal image) must be recognised as associates representing two images of the same dot. However, this diplopic pair would have to be recognised from among a large number of incorrect but equally likely dot pair possibilities (this is the ambiguity problem[2] which lies at the root of the distinction between local and global stereopsis). Apart from the subjective appreciation of diplopia, correct dot pairings are needed to generate the correct magnitude and direction for compensatory vergence movements. Moreover, subjective diplopia seems not to occur when random-dot patterns are not fused. A rivalry avoidance mechanism could be postulated, but again this could not provide information for compensatory vergence movements of the correct magnitude and direction.

To summarise, extended monocular contours and diplopia are not essential to the production of fusional vergence amplitudes. Our results confirm previous reports of vergence amplitudes with random-dot targets.[1-6] We have extended these findings by showing that (1) the reported vergence amplitudes are not artefacts of monocullar contours which arise from target borders or the testing apparatus, (2) vergence amplitudes can be produced by dynamic random-dot stereograms and are therefore not the result of an optokinetic vergence response to a shifting field of dots, and (3) while initial fusion of random-dot targets may be more difficult than fusion of targets with monocular contours,[7,8] once fusion has been obtained the motor 'fusion lock' is equally robust and can maintain fusion over the same range of vergence angles.

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Posterior chamber intraocular lens implantation—a new forceps to simplify capsular bag fixation

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SUMMARY The case for capsular bag fixation of the Sinsky-Kratz type of posterior chamber intraocular implant lens is presented, and the various methods in use to position implant lenses are outlined. The new forceps are described and the rationale for their adoption and use is given in an illustrated, step-by-step fashion. Their additional use in anterior chamber intraocular lens implantation is mentioned. There is a brief summary of the author's experience with this instrument.

This paper presents an instrument based on a new design concept which simplifies the insertion of posterior chamber intraocular implant lenses. It has also proved useful in positioning anterior chamber lenses of certain designs.

Extracapsular cataract extraction (ECCE) is increasingly accepted as the best method of management of cataract, particularly in patients for whom intraocular lens (IOL) implantation is planned. So safe is the procedure of extracapsular cataract extraction and posterior chamber intraocular lens implant (ECCE and PCIOL), in terms of sparing of corneal endothelial cells and the absence of surgical complications[1-3] that the minimum age for lens implantation is falling, and some surgeons are prepared to undertake this procedure for carefully selected patients of 30 years or younger.

The three principal aims of ECCE and PCIOL technique are: (1) to minimise intraocular instrumentation; (2) to limit corneal bending; (3) to implant in such a way as to minimise deleterious interaction between lens and ocular tissues (some authorities would add that this is best achieved by intracapsular IOL fixation—bag fixation. Bag fixation is the most physiological position for the pseudophacos and its advantages are increasingly well documented.[4-7]

Description of instrument

The forceps illustrated are for right-handed surgeons; a left-hander would require a mirror image instrument. Their design embodies unique features. A small soft action forceps body of surgical stainless steel (Fig. 1A) resistant to torsion was chosen. The jaws have two bends, the most proximal such that the jaws face forwards with the handle held in the palm between forefinger and thumb. At this bend there is an offset so that the action of the tips is a slide rather than a pure apposition. The tips of the forceps (Fig. 1B) are hooked downwards at 90°. The upper, anterior jaw has a shallow notch cut horizontally close to the tip to enable a 0·4 mm loop (haptic) to be grasped. The lower, posterior jaw is polished and profiled to act as a ramp to deflect the loop posteriorly as well as superiorly as it is released (patient in the anatomical position). The posterior jaw's hooked shape also acts as an iris and capsule retractor if necessary.

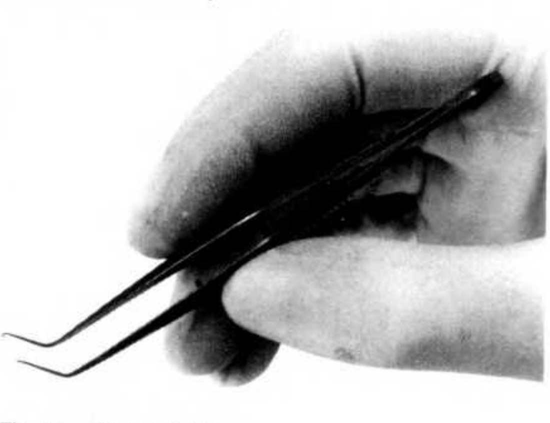

Fig. 1A *The new forceps.*

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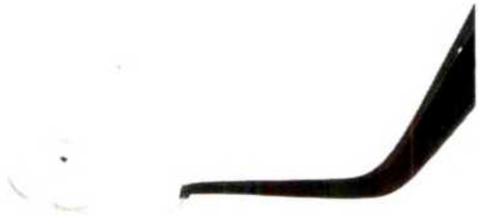

Fig. 1B *Detail of the tips grasping an IOL loop.*

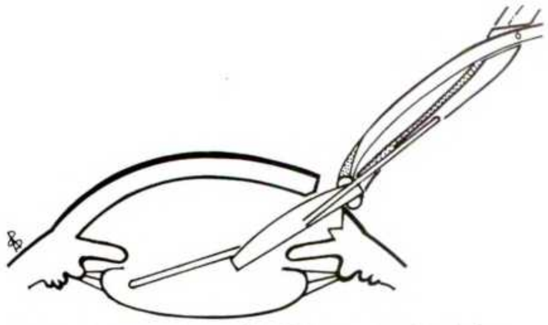

Fig. 2 *The inferior loop of the IOL positioned in the bag with Clayman's forceps.*

The chief advantage of these forceps over current designs[8,9] is that bag placement of the PCIOL is possible with a one-handed technique[10,11] and dialling is avoided.

Use of instrument

A routine extracapsular cataract extraction is performed. I prefer a corneal section placed just anterior to the limbal vascular arcades, but surgeons using a corneoscleral approach will find the forceps similarly useful. The anterior chamber is deepened with viscoelastic fluid to open as far as possible the fornices of the capsular bag. The IOL is presented to the section held either conventionally in Clayman's forceps (Fig. 2) or the author's forceps turned upside down, and the lower loop is passed across the anterior chamber, steeply angled so that the apex of the loop glides over the posterior capsule (with care if a 1° posterior capsulotomy has been fashioned) until it rests in the inferior capsular fornix. The lens is released before the forceps enter the eye, and the apex of the upper loop is grasped with the implant forceps, the loop being engaged in the groove of the anterior jaw (Fig. 3). By advancing the forceps into the anterior chamber both loops are compressed until the optic lies behind the pupillary aperture and the apex of the upper loop will pass behind the iris (Fig. 4). Note that by holding the upper loop rather than the optic for this part of the manoeuvre the elasticity of both loops comes into play, and the risk of zonular dehiscence or capsular rupture is minimised.

The surgeon rotates the forceps between finger and thumb, steepening the angle of the jaws and using the point of entry into the eye as the centre of rotation, taking care not to open the section or bend the cornea. This allows the superior loop to slide away from the jaw of the forceps and retracts the iris and anterior capsular remnant if necessary (Fig. 5). When the loop is released the posterior jaw acts as a chute diverting it into the upper bag fornix. Fig. 6 shows the correct position of the lens following removal of the forceps. A bag fixated IOL will require no formal dialling to centre it. Gentle nudging with the tip of the dialling hook to ensure the posterior capsule is well stretched and not puckered is sufficient.

When the anterior chamber is reformed, the bag fixated IOL will be seen to lie very posteriorly,

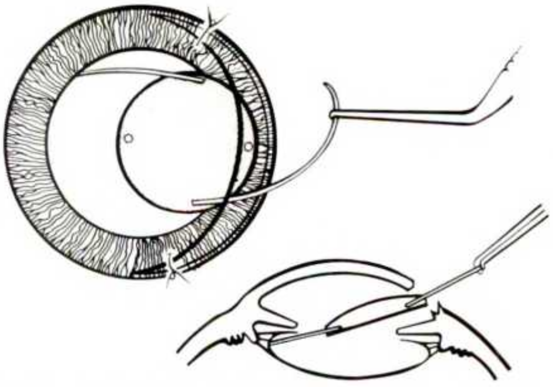

Fig. 3. *Method of grasping the superior loop.*

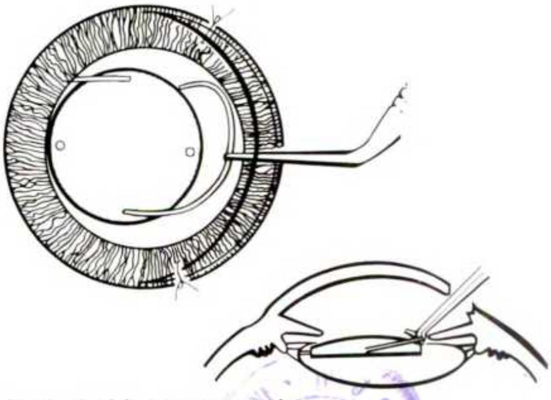

Fig. 4 *Both loops compressed.*

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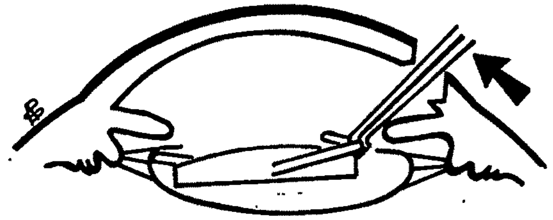

Fig. 5 *Steeping the angle of the jaws before releasing the loop.*

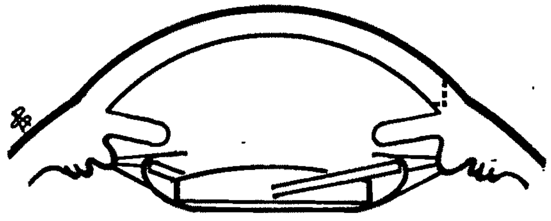

Fig. 6 *Correct positioning of a bag fixated IOL.*

allowing a clear gap between iris and optic in most eyes.

Experience with instrument

The author's experience with this instrument consists of a series of 150 posterior chamber Sinsky-Kratz style implant lenses of various manufacture, the last 73 of which were intended to be bag fixated. Three implants were of the Arnott AR4 type, and one was a closed-loop Sheets design. Seven patients had 1° capsulotomy immediately prior to implantation for central capsular fibrosis. Two patients' implants were inserted as 2° procedures and bag fixation was naturally not possible. Of the 73 lenses intended to be bag fixated, 68 appeared on the table to be successfully placed, and one further patient subsequently appeared by three-mirror Goldmann lens examination through fully dilated pupil to have a sulcus fixated lens.

One highly myopic patient, having had a sulcus fixated (+6·0D) IOL, failed to achieve IOL fixation, and at six weeks the IOL was freely mobile in the retropupillary anterior segment. This was removed without difficulty and without affecting visual acuity; the eye had macular myopic degeneration.

The position of all lenses was confirmed within the first six weeks following surgery, by which time loops of the bag fixated IOLs were firmly encased within the adherent capsular leaves. All bag fixated IOLs appeared well centred; no dialling holes or edges of optics were visible through undilated pupils.

The versatility of this instrument allows its use in the placement of the upper loop of semiflexible or semirigid open loop anterior chamber IOLs such as the Novaflex, Optiflex, or Multiflex type. The author has performed only a small number of anterior chamber implants, but sufficient to confirm the instrument's usefulness in this type of surgery in placing the superior loop without excessive pressure on the inferior angle structures.

In conclusion this instrument has been designed specifically to meet the needs of superior loop placement of the Sinsky-Kratz posterior chamber IOL with minimal intraocular manipulation, and it facilitates capsular bag fixation, which can be reliably achieved with a one-handed technique. No torsional force is applied to the lens as with conventional technique, and the danger of inadvertant IOL-endothelial touch is avoided. Dialling is unnecessary, and iris trauma is minimised.

The longer follow-up of the series of patients in whom bag fixation of the IOL was attempted will be the subject of a further report.

I acknowledge with gratitude the assistance of the consultant staff of Whipps Cross Hospital Eye Unit: Mr J S Conway, Miss M T Challis, and Mr B Beveridge, whose patients comprise my series; Mr A D McG Steele for his constructive criticism; Miss Karen Johnston and Mr Max Brown of the Medical Illustration Department, Moorfields Eye Hospital.

The implant forceps are commercially available from Osborne and Simmonds, London EC1R 0AT. My thanks to Mr H Simmonds for his work on this instrument.

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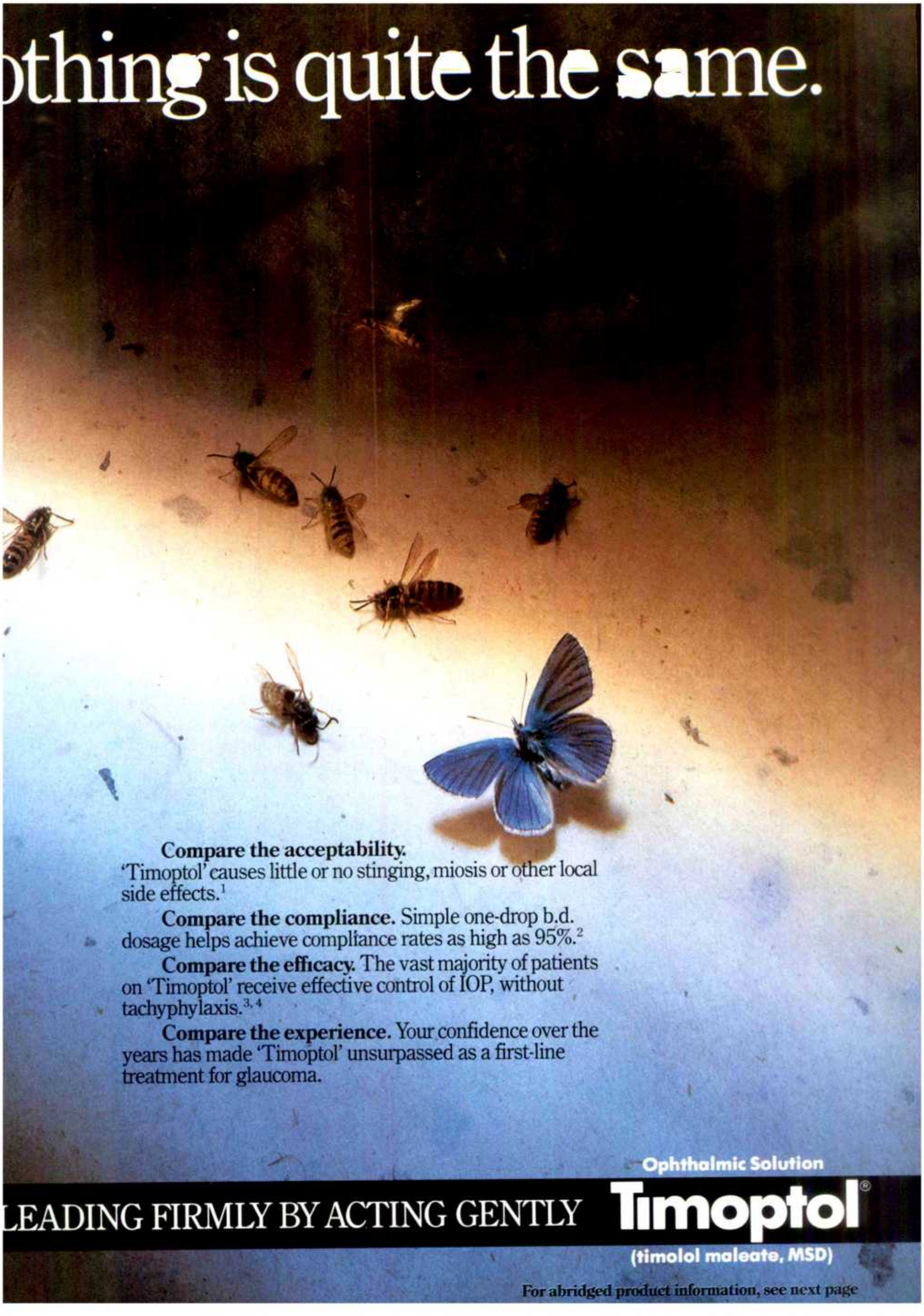

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British Journal of Ophthalmology, 1986, **70**, 727–731

Past, present, and future surgical management of malignant epithelial neoplasms of the lacrimal gland*

JOHN WARREN HENDERSON

From Louisiana State University Medical Centre, Louisiana, USA.

It is a once in a lifetime honour to receive an invitation to present the Mustardé lecture, and it gives me a feeling of great inner warmth to fulfil this role at the fourth annual meeting of your society.

Your first president, Mr John C Mustardé, is a ubiquitous man with an outgoing personality who has probably lectured in all principal regions of the world except, possibly, the South Pole. When I received the invitation I had some misgiving that I could find a suitable subject in your speciality that had not already been addressed by Mr Mustardé in his thorough, inimitable style. However, a search of his extensive bibliography did not reveal any publication on the subject of malignant lacrimal gland tumours.

A treacherous neoplasm

This family of neoplasms has bedeviled me throughout my career-long love affair with orbital tumours. In the coverage of the subject today I have selected the adenoid cystic carcinoma as the prototype of the group, and I will direct most of my remarks to the management of this treacherous neoplasm. It is the most frequent and most malignant member of the malignant neoplasms intrinsic in the lacrimal gland. If we can find a cure for adenoid cystic carcinoma, the management of the other malignant epithelial tumours of the lacrimal gland will be a lesser challenge.

I also fear adenoid cystic carcinoma of the lacrimal gland because I consider it the most evil of all primary neoplasms of the orbit. Personally, I would rather take my chances of survival with malignant melanoma of the orbit than my chances of survival with adenoid cystic carcinoma. I have never cured a patient with this particular neoplasm nor have I personally observed a well documented cure among patients managed elsewhere.

The term, adenoid cystic carcinoma, came into general usage about 30 years ago, at which time it was separated histologically from other epithelial neoplasms of the lacrimal gland and given free standing status among this family of tumours.[1 2] However, the surgical management of this tumour precedes by several years the first study of the neoplasm with the microscope.

The past

An early in-depth account of this neoplasm is that of Theodor Billroth.[3] Billroth, aged 27, was an assistant in B R K Langenbeck's surgical clinic in Berlin when he published his study on multiple recurrences of the tumour from the same patient. Using the solvents and fixatives of his era, he was intrigued by a system of glass-clear compartments and knobs in the residue of the tumour that he believed was the stroma of the tumour. These amorphous compartments were long and narrow, and from this he derived the name cylinder tumour. Billroth's observations were later confirmed when similar tumours were studied under the mircoscope 10 to 15 years later. Billroth's name for the tumour, cylindroma, persisted for almost 100 years.

Billroth's patient was a 22-year-old man who underwent seven operations in an interval of 2½ years. First, the tumour was removed. Soon the eye was enucleated because of recurrent tumour. Next several exenterations were performed. Finally, portions of the orbital bone were cauterised with a hot iron. However, the tumour stubbornly recurred. Throughout this ordeal the sedatives and analgesics of that era had little effect on the patient's pain. By the time of the last operation the tumour had extended into the ethmoid bone, the pterygopalatine fossa, and filled the adjacent maxillary antrum. In the few weeks before death the patient became insane, probably from intracranial extension of the tumour.

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All the salient clinical frustrations in the management of this tumour are found in Billroth's description of this pitiful patient in 1856, and these frustrations are equally applicable to the patients of the present time. Even so, the latter undergo fewer operations, control of pain has improved, general anaesthesia is available, and palliative radiotherapy permits longer survival, but the fatal result today is nearly as frequent as it was over a century ago.

More radical surgery

For almost the first hundred years cylindromas were managed in a fashion similar to that of Billroth's patient and many surgeons confirmed the frequency of bone invasion by the tumour. However, removal of diseased bone was attempted only in cases of recurrent tumour. In such cases the bone usually was nibbled away in stages over a period of several operations. A more radical removal of orbital bone that resulted in exposure of the dura was shunned because of the high risk of sepsis, meningitis, and death.

Reese and Jones in 1964 expressed the corollary that, if the invasion of bone by recurrent tumour is so frequent, then the initial surgery should be more radical. They proposed the removal of the lateral wall and rim of the orbit, combined with an exenteration, earlier in the course of the disease than had previously been attempted (Fig. 1).[4] At the time of their report this surgical procedure had been used on five patients with lacrimal gland neoplasms. Two of these five cases were adenoid cystic carcinomas. In all five patients their combined bone removal-exenteration procedure was not performed until the malignant nature of the neoplasm had been established by study of fixed tissue specimens. In essence this operation was the second surgical procedure on the patient that followed, at some variable interval, the initial surgical biopsy.

In the 20 years since the report of Reese and Jones[4] many, surgeons have used their operation, or some modification, to eradicate malignant neoplasms of the lacrimal gland. To learn the effectiveness of this operation for adenoid cystic carcinoma I searched the literature for well documented cases that had passed a 10-year disease-free interval from the time of initial surgery, but I found no reports of survivors of this type. Also I recently wrote to several dozen physicians whom I knew were interested in the survival of patients with adenoid cystic carcinoma, and physicians who had been in practice long enough to have personal knowledge of patients who had undergone the Reese-Jones type of operation for the disease. Those who submitted data in response to my inquiry are listed in Table 1. From this mail survey I found only one case that seemed to meet the minimal criterion of a 10-year disease-free interval.

This survivor was a patient of Dr Robert Byers, of Houston, Texas. The patient, a 61-year-old woman, had a biopsy of an adenoid cystic carcinoma of the lacrimal gland in 1965, and has been followed up for a

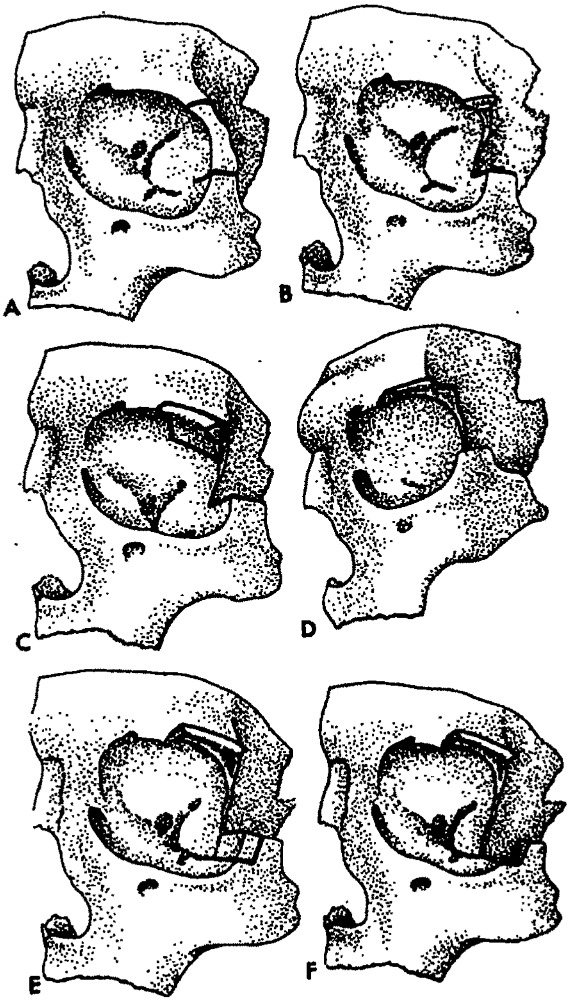

Fig. 1 *Resection of orbital wall during exenteration.*
A: *Bone resection is begun by cuts through lateral wall above and below with Stryker saw, as in Krönlein operation.*
B: *Bone flap is broken posteriorly and removed and remaining broken edge is rongeured away as far posteriorly as possible.* C: *Bone resection is continued in area of lacrimal fossa by Stryker saw cut that is parallel to orbital rim and extends to mid point of superior rim.* D: *Broken posterior edge is removed with rongeurs as is necessary.* E: *Bone resection continued below by outlining adjacent inferior lateral wall with two Stryker saw cuts.* F: *Resection is completed by removing remaining bone as far as end of the inferior orbital fissure.* (From Reese and Jones.[4])

Table 1 *Physician participants in mail inquiry concerning survival of patients with adenoid cystic carcinoma of lacrimal gland*

Name	*City*	*Name*	*City*
Alper	Washington	Foos	Los Angeles
Beale	Memphis	Jones	New York
Boniuk	Houston	Kennedy	Rochester NY
Bullock	Dayton	Kennerdell	Pittsburgh
Byers	Houston	McCord	Atlanta
Callahan	Birmingham	Reeh	Portland
Carroll	Minneapolis	Smith	New York
Char	San Francisco	Spencer	San Francisco
Cooper	New York	Waller	Rochester MN
Ellsworth	New York	Wilkins	Houston

period of seven years at the time of Byers and colleagues' publication.[5] A short time after the biopsy procedure the neoplasm was removed by an orbital exenteration combined with removal of the lateral wall and rim of the orbit. The resected bone did not show gross evidence of tumour invasion and was not decalcified for histopatholical study, but the neoplasm had extended into the orbital connective tissue. Postoperatively the orbit was treated with radiotherapy.

This patient is living and well approximately 19 years (November 1984) from the time of the original surgery and has not had any local recurrence or metastasis of tumour in that interval (Byers R M, personal communication). The apparent absence of bone involvement by tumour may be one of the major factors in this patient's long survival.

Almost always fatal

Several respondents (Table 1) reported patients who were living 10 to 15 years after surgical diagnosis of their adenoid cystic carcinoma, but in each instance such patients had undergone one or more surgical procedures because of recurrent tumour, or were under therapy for metastasis. I believe such patients are still at risk of death from tumour.

From this type of survey I think it reasonable to assume that adenoid cystic carcinoma is almost always fatal. I believe a major factor in this dismal prognosis is that, over the years, we have underestimated the ability of this neoplasm to penetrate bone early in its growth. This penetration may be so insidious that it may be visible neither by radiography nor by gross inspection of bone. It is also my theory, but I have no clinical proof, that adenoid cystic carcinoma disseminates faster in bone than in soft tissue.

Once the tumour penetrates bone there are no tissue histiocytes or macrophages that might resist the spread of neoplasm along the marrow cavity of bone. In contrast the orbital soft tissues of some patients seem to resist the infiltration of tumour with a barrier of fibrosis and sclerosis. If tumour dissemination in bone is easier than tumour spread along the fascial planes of soft tissue, this is the reason why the limited bone removal of the Reese-Jones procedure may not cure the malignancy if bone invasion already is present at the time of the definitive surgery.

This point is illustrated by the course of a patient whose adenoid cystic carcinoma was removed by the combined Reese-Jones technique and followed up for a number of years. This patient was also treated with postoperative radiotherapy. (Jones IS, personal communication). The course of the patient in the eight years following surgery and radiotherapy was uneventful. The exenterated orbit remained clean without sign of local recurrence of tumour. Suddenly, the patient developed fainting spells, loss of equilibrium, and died shortly thereafter. Necropsy revealed neoplasm in the brain adjacent to the treated orbit, probably due to direct extension of tumour that was present in bone beyond the boundary of the original surgical resection. The postoperative radiotherapy probably had had some suppressive effect on the multiplication of neoplastic cells in the eight-year interval of survival.

Removal of bone

If tumour dissemination through bone is a greater hazard than soft tissue infiltration in the ultimate course of the patient, it seems logical that bone should be removed at the time of the initial surgical procedure rather than some interval after either incisional or excisional biopsy. Accordingly a colleague and I proposed in 1976 an en bloc removal of the carcinoma and underlying bone as the initial surgical procedure.[6] Alas, in this patient histological study revealed extensive infiltration of tumour along the margin of the bone specimen, suggesting tumour dissemination beyond the area of bone resection. This patient ultimately died from metastasis.

Thirteen years ago Murray and colleagues also addressed the problem of removal of orbital bone in their publication on cranio-orbital resection.[7] Other surgeons prior to this time had described radical removal of orbital bone for neoplasms secondarily invading the orbit from the sinuses, face, intracranial vault, and temple, but the Murray group was one of the first to target their procedure for primary orbital disease. Subsequently others have used the cranio-orbital procedure for neoplasms of the orbit but have modified the operation both in the extent of bone removal and the method used to reconstruct the surgical defect. Basically all these operations remove more orbital bone and soft tissue in a monobloc than

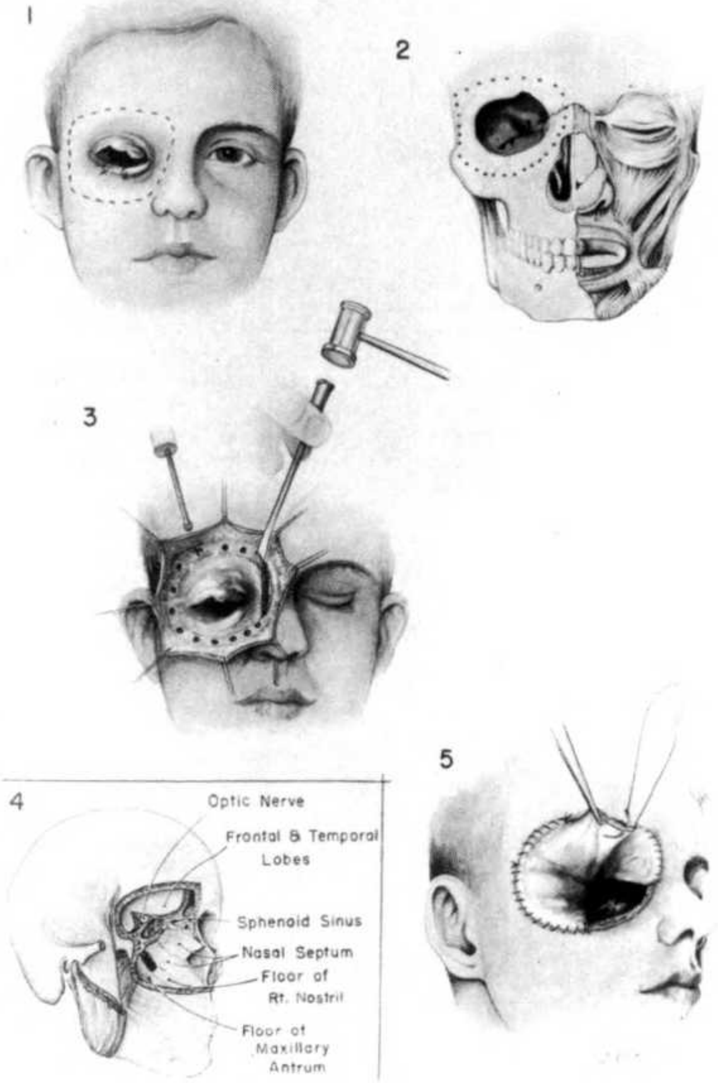

Fig. 2 *Operative technique of regional cranio-orbital resection. 1: A circumorbital skin incision is made around the soft tissues and is carried down to periosteum. 2: The periosteum is elevated and multiple drill holes are made in frontal, nasal, malar, and maxillary bones. 3: The multiple burr holes are connected with the use of an osteotome. At this point the dura mater is separated from bone which encases the tumour. 4: Anatomical structure of the defect created by the surgical resection. Note that all structures between the frontal lobe and palate are expendable, once the eye has been removed. 5: The defect is resurfaced with split thickness skin graft.* (From Murray *et al.*[7])

once thought possible, and the surgery is often performed by a team of surgeons from different surgical disciplines.

In the procedure of Murray *et al.* a circumorbital incision is made through skin down to periosteum (Fig. 2). Next, the periosteum is elevated. Multiple burr holes are drilled in the frontal, nasal, maxillary, and malar bones and the holes are connected with an osteotome. Then the bony box containing the tumour is separated from the adjacent dura. After severing the optic nerve anterior to the chiasm, all tissues from the frontal lobe to the palate are delivered as a monobloc. Monobloc resections of this general type are now used as the primary procedure for the removal of malignant neoplasm of the lacrimal gland in some tumour centres.

One such case of this type with a follow-up interval of seven years was reported by Wright in 1982.[8] The patient, a 56-year-old man, underwent a monobloc removal of an adenoid cystic carcinoma of the lacrimal gland and the surrounding bone in March 1974. Histological study of the tissue specimen showed tumour extension into surrounding connective tissue, the lacrimal gland fascia, and the periosteum of the orbital roof, but there was no evidence of bone invasion (Wright J E, personal communication). Normal haemopoietic marrow was seen in one section of bone.

The patient was still tumour-free and in good health in September 1984, an interval of 10 years 5 months from the time of original surgery (Wright J E, personal communication). The role of the monobloc procedure in effecting this apparent '10-year cure' would be more positive if there was histological evidence of tumour invasion of bone in the surgical specimen. If there was no marrow invasion by tumour in any of the bone not decalcified for histological study, an exenteration of the orbit might have sufficed for Wright's case.

Several respondents to my mail inquiry (Table 1) also mentioned a few additional cases of adenoid cystic carcinoma that had undergone the monobloc bone-tumour resection procedure, where tumour invasion of bone was confirmed by histological study of the tissue specimen. However, the tumour-free interval of these cases has not yet approached 10 years. At present I believe a tumour-free interval of 10 years is the minimum to permit cautious consideration of a cure of adenoid cystic carcinoma.

The Future

On the basis of the cases cited above there seems reasonable proof that exenteration of the orbit may cure a few cases of adenoid cystic carcinoma of the lacrimal gland provided the neoplasm has not infiltrated the soft tissue beyond the boundary of the dissection, has not invaded bone, and has not metastasised at the time of the definitive surgical excision. Another five to eight years must pass before we can judge the effectiveness of the newer monobloc, tumour-bone dissection procedure in those patients with known tumour invasion of bone.

The challenge of the future is, first, to detect early spread of tumour into orbital bone by techniques superior to the present ones of standard roentgenography, computed tomography, and gross inspection of bone. This would determine whether orbital bone resection, in addition to exenteration, is necessary to cure the patients of their neoplasm. Secondly, methods must be discovered to determine the extent of the tumour spread in bone. Such information would determine how much bone removal is needed to encompass the tumour dissemination.

Such discoveries might involve more sophisticated radiosotope scanning of bone than at present available, methods for biopsy of the marrow cavity of orbital bone, or refinements in the nuclear magnetic resonance imaging of orbital bone. The latter provides an image of the marrow of orbital bone heretofore not visualised by other technical methods.

Some of these discoveries or others, not yet foreseen, may be the subject of some future Mustardé lecture.

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Management of ipsilateral ptosis with hypotropia

L A FICKER, J R O COLLIN, AND J P LEE

From Moorfields Eye Hospital, London

SUMMARY Thirty-one patients presented for surgical correction of unilateral hypotropia of the globe and blepharoptosis. The hypotropia and pseudoptosis were corrected by Knapp procedures. The Bell's phenomenon was thereby improved, allowing safe correction of the true ptosis, generally by an anterior levator resection whose magnitude depended on measured levator function.

The association of unilateral ptosis and hypotropia of the globe arises in a number of clinical situations, most commonly in congenital double elevator palsy. Their surgical correction was approached by Beard,[1] who found double elevator palsy in 6% of his cases of unilateral congenital ptoses. He noted levator resection was less effective where superior rectus weakness coexisted, and recommended an additional 4 mm approximately of levator resection. He approached the correction of hypotropia by superior rectus resection and inferior rectus recession with release of the lower lid retractors. Knapp[2] subsequently described transposition of the horizontal rectus tendons to that of the superior rectus. This improved the position of the globe and its elevation. Scott and Jackson[3] recognised, by forced duction tests, that inferior rectus restriction plays a part in some cases and advocated recession of the muscle with release of the lower lid retractors. This was not combined in their work with the Knapp procedure as they feared anterior segment ischaemia. Callahan[4] modified the approach (to reduce the risk of ischaemia) by routinely recessing the inferior rectus combining this with a Jensen[5] style procedure, in which the active horizontal rectus muscles were split and half of each muscle was sutured to the weak superior rectus.

Lee, Collin, and Timms[6] recommend that a forced duction test is done initially. If the eye moves freely, a Knapp procedure alone is done. If there is limitation, the inferior rectus muscle is recessed, and this is combined with a Knapp procedure except in those cases considered to be at risk of ischaemia, that is, those patients over 25 years of age or with a large globe, in whom they do a Callahan procedure. Contralateral superior rectus recession with a Faden procedure is used in selected cases to increase the drive to the paretic superior rectus where these measures prove inadequate. Elevation of the hypotropic globe is considered to be the primary step, followed by correction of the true blepharoptosis, which is the subject of this paper.

Patients and methods

Thirty-one patients presented for surgical correction of unilateral hypotropia of the globe and associated blepharoptosis. The aetiology of the combined abnormalities included congenital double elevator palsy (15 patients), Marcus-Gunn jaw-winking syndrome (eight patients), third nerve palsy (three patients), neurofibromatosis with lid involvement (three patients), and superior rectus sling-induced (two patients).

The surgical approach was to improve active elevation of the globe, thereby enhancing the Bell's phenomenon and correcting the element of pseudoptosis. A Knapp procedure was adopted, elevating the insertions of the horizontal rectus muscles to the superior rectus insertion. In addition any horizontal deviation of the globe was corrected at the same time by appropriate recession or resection of the horizontal rectus muscles, as described by Alvaro.[7] A forced duction test was performed in each case. Inferior rectus restriction, where found, was relieved by inferior rectus recession. Careful recession of the lower lid retractors was performed to preserve normal lower lid position.

The true blepharoptosis was corrected by a levator resection, which was denoted large (greater than 20 mm), medium (15–20 mm), or small. The extent of the resection required depended on the levator

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function (good greater than 10 mm, moderate 4–10 mm, or poor). The minimum delay between these procedures was four months but ranged from four months to two years. An anterior approach was preferred for the large resections, affording good exposure.

CONGENITAL DOUBLE ELEVATOR PALSY GROUP (15 patients)

Five patients had previously undergone both vertical muscle surgery (inferior rectus recession, superior rectus resection, or both) and ptosis surgery. Three patients had undergone vertical muscle surgery alone and three ptosis surgery alone. Hence, four of the 15 were cases not previously operated upon. Of the patients previously operated upon one required a mucous membrane graft to his scarred upper fornix and two required scleral grafting to raise adequately the lower lid following inferior rectus surgery. A Knapp procedure was indicated in all patients in this group with additional inferior rectus recession in only two. In one case inferior rectus recession was supplemented by a contralateral superior rectus recession with a Faden procedure. Horizontal rectus recession or resection was performed simultaneously with a Knapp procedure in seven cases. Two patients were mainly concerned by their ptoses and elected not to undergo strabismus surgery.

The ptoses were corrected as follows. One patient with no levator function underwent bilateral brow suspension. Eight had a large anterior levator resection, one a moderate anterior levator resection, and five small resections by either an anterior or posterior approach.

JAW-WINKING GROUP (8 patients)

Six patients were found to require a Knapp procedure and one a Callahan operation with inferior rectus recession. A severely retarded child, in whom ptosis correction was the only cosmetic goal, had a large posterior levator resection without extraocular muscle surgery.

Where ptosis was the major problem, an anterior levator resection was performed. Two patients had a large anterior levator resection and one a cautious levator resection rather than a brow suspension, as the Bell's phenomenon was not adequately enhanced by the Knapp procedure. Significant jaw-winking was corrected by levator excision and bilateral brow suspension. Three patients required bilateral brow suspension and another is yet to undergo ptosis surgery. The last patient declined ptosis surgery, being satisfied after the Knapp procedure.

THIRD NERVE PALSY GROUP (3 patients)

The first patient had a post-traumatic third nerve palsy with misdirection regeneration. The condition had been stable for five years. A Knapp procedure with lateral rectus recession and medial rectus resection was supplemented by inferior rectus recession. Later contralateral lateral rectus recession with a Faden procedure and medial rectus resection were performed to encourage medial rectus drive of the affected eye. Levator function was good, and a small posterior levator resection was finally done on the affected side with a contralateral upper lid recession.

The remaining two patients had congenital third nerve palsies. One had previously undergone both vertical muscle surgery and ptosis correction. Both had moderate levator function. They underwent Knapp procedures, achieving only reduced Bell's phenomena. Large anterior levator resections were subsequently carried out.

NEUROFIBROMATOSIS (3 patients)

Debulking of the plexiform neuromata preceded correction of hypotropia and ptosis in two cases. One patient had a good Bell's phenomenon with reasonable elevation of the globe and underwent anterior levator resection alone. Of the other two, one had a Callahan procedure with inferior rectus recession prior to a large anterior levator resection and further debulking. The third had a Knapp procedure with inferior rectus recession. This was followed by upper lid debulking and canthal raising plus a dacryocystorhinostomy. Prior to a large anterior levator resection, lower lid scleral grafting was required to lengthen the lower lid retractors.

SUPERIOR RECTUS SLING INDUCED (2 patients)

Both patients presented with ptosis and hypotropia following surgery elsewhere at which the superior rectus muscle had been attached to the upper eyelid to elevate it. One case in which the original ptosis was acquired following trauma required division of the superior rectus sling first, to restore proper superior rectus function. The levator disinsertion was then corrected via an anterior approach. The other case was of congenital ptosis. A Knapp procedure was performed followed by a large anterior levator resection, with freeing of all the adhesions of the previous superior rectus sling operation.

Results

CONGENITAL DOUBLE ELEVATOR PALSY GROUP

The correction of blepharoptosis may be considered in terms of both pseudoptosis and real ptosis. Following the Knapp operation as described by Lee *et al.*[6] successful active elevation of the globe is accompanied by correction of the pseudoptosis and improvement of the Bell's phenomenon. This was

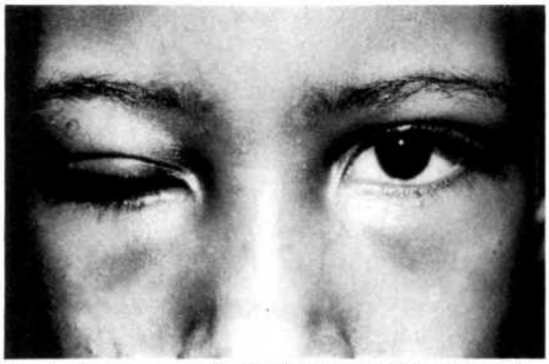

Fig. 1 *Primary gaze showing hypotropia of the right globe and blepharoptosis.*

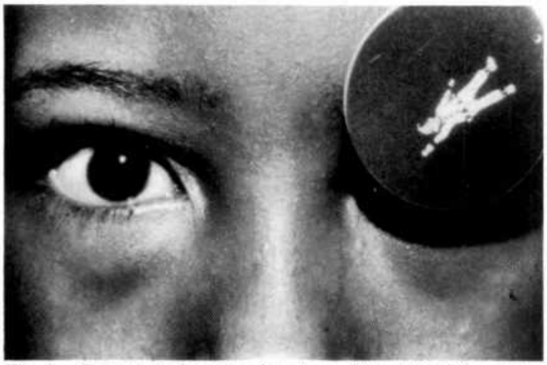

Fig. 2 *Cover test showing elevation of the right globe with correction of the pseudoptosis.*

achieved in three of the four cases not previously operated on; these patients underwent Knapp procedures and had good levator function. The fourth patient had poor levator function and gained improvement rather than correction of the hypotropia and pseudoptosis. Eight patients had previously undergone surgery to the vertical rectus muscles with no improvement of the hypotropia, pseudoptosis, or Bell's phenomenon. These were satisfactorily corrected by a Knapp procedure in six of the eight cases. The remaining two had considerable scarring round the common sheath, but were improved. Three patients had undergone ptosis surgery with residual ptosis, pseudoptosis, and hypotropia. Correction of the pseudoptosis and elevation of the globe were achieved by Knapp surgery.

The element of real ptosis was corrected to within 1 mm, with acceptable cosmesis, in 13 cases with surgery based on the guidelines relating levator function to the amount of levator resection required.[8] Where a large resection was indicated, it was facilitated by the good surgical exposure gained via an anterior approach.

Two patients had a measured overcorrection, one of whom needed an upper lid recession. Two of the 13 patients, who had cosmetically good results with lid levels within 1 mm of each other, had a functional overcorrection reflected by punctate corneal staining. These were asymptomatic and treated conservatively with lubricants.

JAW-WINKING GROUP

Of the six patients who underwent primary Knapp or Callahan procedures one was cosmetically satisfied and had good levator function. Of the three requiring levator resection, one was corrected despite the complication of orbital asymmetry due to a basocranial teratoma. The second had been unsuitable for brow suspension in the absence of an adequate Bell's phenomenon. The third is yet to undergo ptosis surgery. Two patients with signficant jaw-winking were corrected by brow suspension and levator excision procedures. Two patients underwent levator resection alone (including the retarded child) and were found to have residual pseudoptosis requiring a Knapp operation.

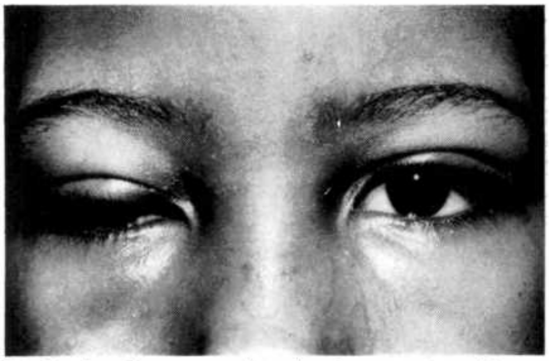

Fig. 3 *Post-Knapp procedure showing correction of the hypotropia and revealing the true blepharoptosis.*

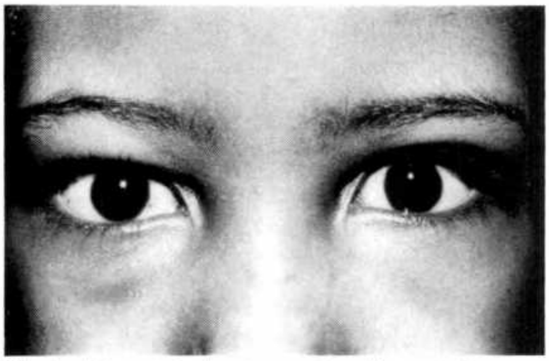

Fig. 4 *After anterior levator resection, demonstrating symmetry of globes and lids.*

THIRD NERVE PALSY GROUP

The Bell's phenomenon was not markedly improved in this group. After the Knapp operation, supplemented by contralateral superior rectus surgery, as described above in the case with misdirection regeneration, levator resection achieved a satisfactory eyelid elevation correcting the lid levels to within 1 mm of each other. The incidence of punctate corneal staining was high in this group, as the Bell's phenomenon was characteristically poor. This was particularly marked in the case with misdirection regeneration, whose poor ocular movements had necessitated bilateral strabismus surgery. However all the patients were young, with good tear production, and have tolerated the punctate staining with the aid of lubricants over a three-year follow-up period.

NEUROFIBROMATOSIS

The ptosis was completely corrected in one case. A 50% improvement of the ptosis was achieved in the other two cases. Residual bulkiness of the lid and some hypotropia of the globe remained in all cases.

SUPERIOR RECTUS SLING-INDUCED GROUP

The ptosis was corrected to within 1 mm and the hypotropia was almost completely corrected in both cases. There was a residual minimal vertical diplopia in the post-traumatic case.

Discussion

The group with congenital double elevator palsy illustrates the principles involved in the management of combined hypotropia and blepharoptosis. In the presence of good levator function, pseudoptosis tends to account for much of the blepharoptosis and may be corrected by a Knapp procedure alone. Two such patients did not require further surgery, and two required a small posterior levator resection. Beard[9] reported a lack of impressive improvement using a Knapp procedure alone. Our experience suggests that this depends on the levator function.

Pseudoptosis may be difficult to assess in young children, particularly where fixation by the affected eye is poor, secondary to amblyopia. Where the magnitude of the pseudoptosis is in doubt, it should be assumed to exist in the presence of a hypotropic globe. The globe should be elevated first with a Knapp procedure before ptosis surgery is performed.

Satisfactory elevation of the globe and improvement of the Bell's phenomenon was achieved in all four cases not previously operated on, including one with a large deviation (55 dioptres). Patients who had previously undergone surgery to the vertical rectus muscles were not corrected until a Knapp operation was performed. Full correction of blepharoptosis can safely be planned only in the presence of an adequate Bell's response, and in our experience the Bell's phenomenon was usually improved after a Knapp procedure. The magnitude of levator resection can be reduced where exposure problems are anticipated, as in the absence of a good Bell's phenomenon.

Inferior rectus recession may cause lower lid retraction, which can aggravate corneal exposure. It is significant, therefore, that in this series it was not found necessary to recess the inferior rectus in most cases (two out of 15 in the congenital double elevator palsy group). This emphasises the importance of preoperative assessment by means of the forced duction test in deciding upon inferior rectus recession. The age factor, with respect to anterior segment ischaemia, must be borne in mind when considering disinsertion of more than two extraocular muscles. Most patients in this series ranged from 3 to 18 years of age, but one aged 23 underwent an uncomplicated Knapp procedure with simultaneous inferior rectus recession without ischaemic problems.

Inferior rectus recession was routinely performed by Callahan[4] and inferior rectus retraction requiring recession was reported in 73% of cases by Scott and Jackson.[3] The need for this high rate of inferior rectus recession was not confirmed in this series.

The management of the ptosis in patients with jaw-winking has received much attention.[10] This series points to the relatively high incidence of jaw-winking in patients presenting with a ptosis and hypotropia (25%) and should alert the ophthalmologist to look for the Marcus-Gunn phenomenon in all patients presenting in this way. The importance of extraocular muscle surgery in achieving symmetry of the eyes and an improved Bell's phenomenon cannot be overemphasised, as this governs the type of ptosis surgery which is subsequently indicated.

The cases with third nerve palsy illustrate the importance of normal horizontal rectus muscles in the achievement of good results following Knapp procedures. The patient with misdirection regeneration required supplementary contralateral surgery to the horizontal rectus muscles with a Faden procedure on the lateral rectus to increase adduction of the affected eye. This in turn aided active elevation of the hypotropic globe. Poor elevation of the globe limited the amount of levator resection it was safe to perform. Symmetry was therefore achieved by a planned, small, ipsilateral levator resection combined with contralateral upper lid recession. Both patients with congenital third nerve palsy were found to have persistently poor elevation following their Knapp procedures. They did not suffer from exposure problems, despite full correction of their true ptosis, but it should be remembered that tear production is generally adequate to compensate in young patients.

The patients with neurofibromatosis have a continuing problem with recurrence of abnormal lid tissue during the growing period. Thus debulking must often be repeated. The levator is often grossly infiltrated, such that measurement of a resection is inaccurate. The globe may be buphthalmic as well as hypotropic. A Callahan procedure was preferred in one case because of the large abnormal globe, which was at risk of ischaemia. Levator resection following either a Callahan procedure or a Knapp operation achieved good results in two patients. The third patient was educationally subnormal, and debulking with levator resection provided a satisfactory result.

The last two cases show that the superior rectus may be weakened mechanically by a superior rectus sling which incompletely corrects the original ptosis. The management follows the same general principles of active elevation of the globe and levator surgery. Thus removal of the sling with division of adhesions to the superior rectus was the first step, and it could be supplemented by a Knapp operation. This was followed by appropriate levator surgery—reinsertion in the traumatic case and resection in the congenital ptosis case.

In summary, hypotropia, ptosis, and levator function must be assessed carefully. Surgical correction is best achieved by the logical sequence of a Knapp procedure followed by levator resection. This eliminates the confusion introduced by pseudoptosis and provides a bonus safety factor of an improved Bell's phenomenon at the time of lid raising. Horizontal deviations are conveniently corrected by modifications of the Knapp procedure. Inferior rectus recession is seldom required, and it is known to increase complications related to the lower lid position and normal lid closure. Superior rectus resection when the muscle is known to be weak is illogical and unhelpful. It can be associated with disturbance of the upper fornix, which may require mucous membrane grafting. Superior rectus surgery is said to impair levator function, since the attachment of the common sheath is interfered with. This may make the ptosis worse, often without any significant effect on the position of the globe. After a Knapp procedure a levator resection may be quantified and reliable ptosis correction thereby achieved. A brow suspension may be substituted where levator function is very poor or in jaw-winkers in whom the levator muscle is excised.

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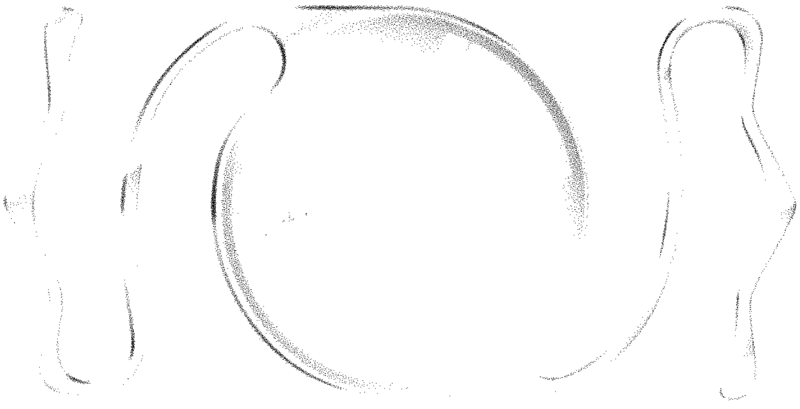

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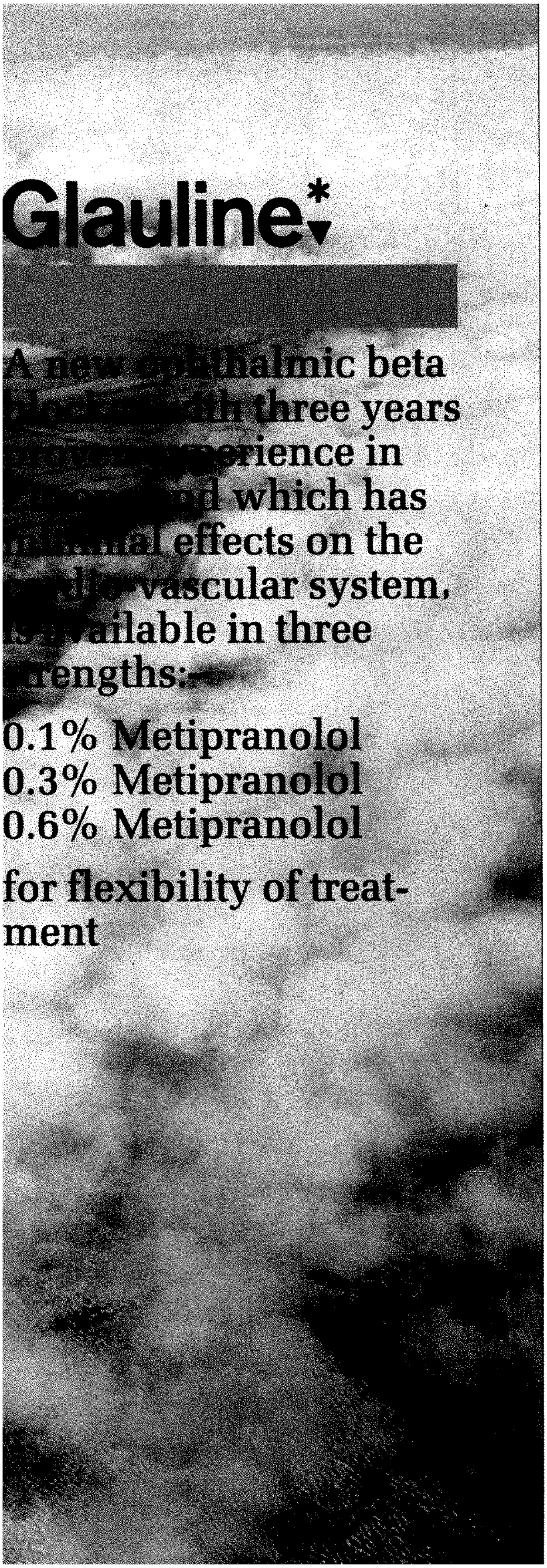
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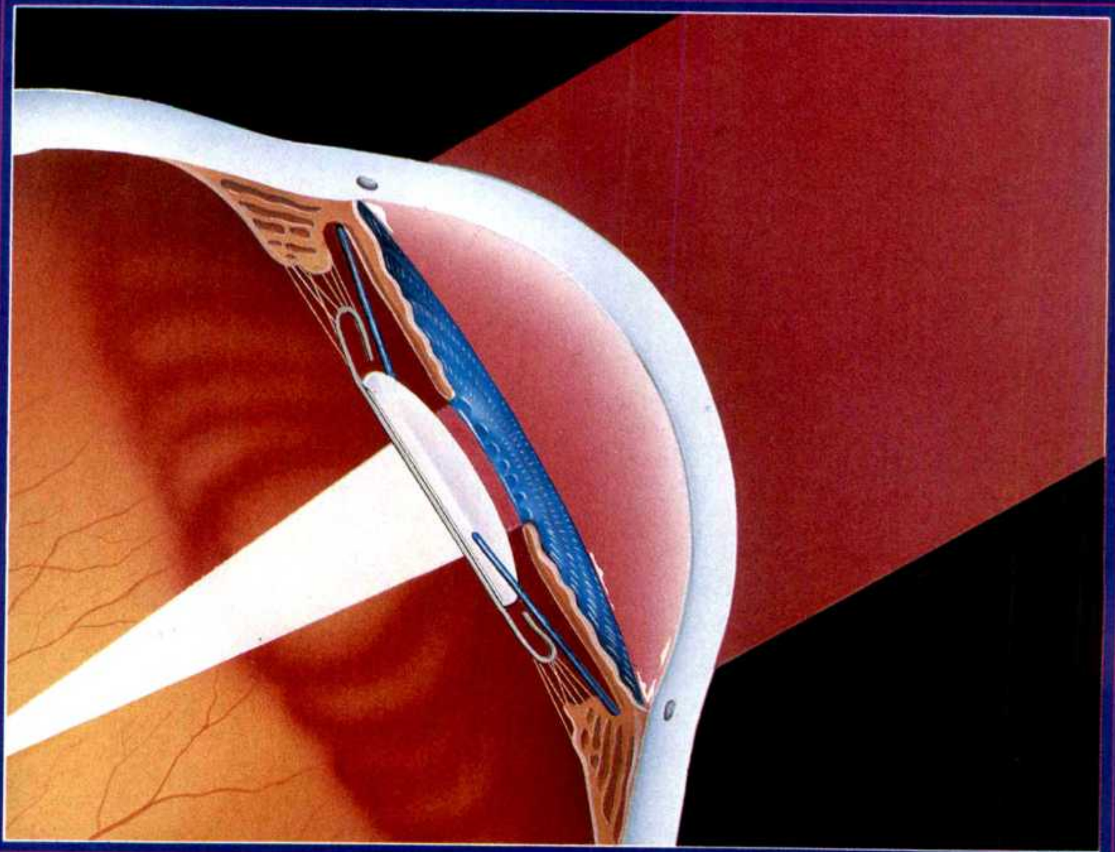

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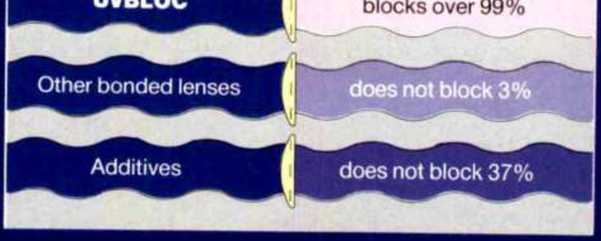

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Regression of Labrador keratopathy following cataract extraction

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SUMMARY Labrador keratopathy (LK) is an acquired corneal degeneration thought to be caused by chronic exposure to solar irradiation. Reports so far suggest that it is a progressive or at least a stationary condition. There are no detailed reports on recommended therapy. A prospective clinical study was conducted to show regression of LK following extracapsular cataract extraction. Seventeen black patients (26 eyes) with LK and mature cataracts underwent extracapsular cataract extraction. The severity of the LK was recorded photographically pre- and postoperatively. The follow-up ranged from 6 to fifteen months. Twenty-four eyes (92%) showed regression of the LK. The reduction in exposure to ultraviolet light as a result of aphakic photophobia could be one of the factors which have led to the regression of the LK.

Labrador keratopathy (LK) is an acquired disease in people who have spent most of their lives outdoors exposed to ultraviolet irradiation.[1-6] Various authors have given different names to the same condition, which is found throughout the world.[2-6] Freedman[2] in his classical paper has shown that the clinical appearances and pathological changes in all cases are similar, differing only in severity. There is an almost unanimous opinion among the authors that climatic conditions and aging are the main factors of this acquired corneal degeneration,[2,3,5-8] whereas histopathological findings are still inconclusive.[3,5,7,9] The work of Johnson[6] has recently contributed to the understanding of the pathophysiology of the formation of the droplets on the superficial cornea. Johnson suggests that solar irradiation acts on plasma proteins present in the cornea, degrading them so that they accumulate in the superficial cornea.[6] Very little has been said on the treatment of LK. Sunglasses and artificial tears are suggested for lesser degree of LK, and for advanced cases superficial keratectomy and lamellar corneal grafts may be indicated.[3,4]

Since LK occurs mainly in the elderly,[2,3,5,6] lens opacities are a common associated finding. Previously we postponed cataract surgery in patients with moderate and severe LK, since visual impairment was predominantly due to the corneal pathology. We therefore did not expect any improvement in vision following lens extraction in patients with preoperative visual acuity of counting fingers or better due to severe LK. In exceptional cases, where bilateral mature cataracts were present and preoperative vision was limited to light perception in both eyes, a cataract extraction was performed.

In September 1983 a 65-year-old black male with a left intumescent cataract and a shallow anterior chamber was admitted for cataract extraction. For the four years prior to admission he had been known to suffer from progressive bilateral severe LK. His right eye had an incipient cataract with 2/60 vision and the left eye had light perception only. A planned left extracapsular cataract extraction was performed.

The patient was discharged after an uneventful postoperative course on betamethasone-neomycin drops (Betnesol N) four times a day, with atropine 1% drops twice daily. Eight weeks later, he returned to our outpatient clinic for routine follow-up. Although he expressed his satisfaction at the improved visual acuity in the left eye, he complained of not being able to sit outside in the sun as had been his habit prior to the operation. On slit-lamp examination there were significant regression of the LK bilaterally. This surprising finding led us to plan a prospective clinical study of the effect of cataract extraction on LK.

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Table 1 *Analysis of 17 patients with LK undergoing cataract extraction*

Number of Patients	17
Number of operated eyes	26
Males	16
Females	1
Age in years	
Range	58–87
Mean	76·4
	No. of eyes
Preoperative staging of LK	
Stage 1	—
Stage 2	3 (12%)
Stage 3	10 (38%)
Stage 4	8 (31%)
Stage 5	5 (19%)

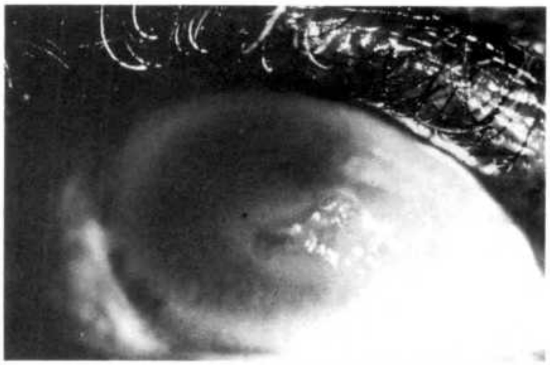
Fig. 2 *Case 3, right eye preoperatively. Note the elevated nodules with corneal ulceration, LK stage 4.*

Materials and materials

Between January 1984 and March 1985 patients with LK and cataracts with best corrected visual acuity of 6/60 or less were admitted for cataract extraction. Patients with other associated diseases such as glaucoma were excluded from the study. Seventeen black patients (26 eyes) were included in the prospective clinical study. All patients except one were males with an age range from 58 years to 76 years and a mean age of 67·4 years (Table 1).

Preoperative photographs of the anterior segments in both eyes were taken with a Zeiss slit-lamp camera. In order to standardise the grading of the corneal pathology the severity of the LK was assessed by the three authors concomitantly according to a modification of Freedman's classification[3] as follows.

Stage 1. Small oil-like droplets are seen in the corneal epithelium, beginning at the limbus in the interpalpebral area. The central corneal epithelium is not yet involved. Vision is not yet impaired. This stage is difficult to demonstrate photographically.

Stage 2. This is characterised by the spreading of these droplets across the cornea to involve the epithelium of the central area and the lower half of the cornea. Vision is 6/12 or less. In some cases there is pigment migration from the conjunctiva on to the cornea in the interpalpebral area.

Stage 3. This is characterised by an increase in the size of the droplets, which begin to invade the deeper part of the epithelium and the superficial parts of the stroma. These droplets now form yellow nodules which protrude above the surface of the epithelium. Vision is 6/24 or less (Fig. 1).

Stage 4. In this stage the nodular swellings erode through the epithelium, causing deep ulcers involving epithelium and stroma. Corneal sensation is diminished or absent in the involved area and vision is severely impaired (6/60 or less). The lesions remain painless and the cornea is not vascularised (Figs. 2, 3).

Stage 5. The corneal lesions become denser and deeper and the involved cornea shows vascularisation which is a result of recurrent secondary infections. Vision is less than 1/60 (Fig. 4).

A planned extracapsular cataract extraction was

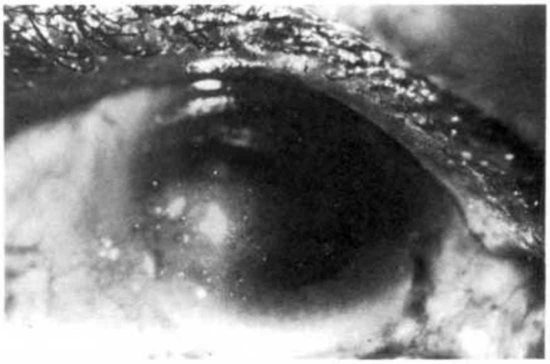
Fig. 1 *Case 17, right eye two days after extracapsular cataract extraction. Note the elevated nodules, LK stage 3.*

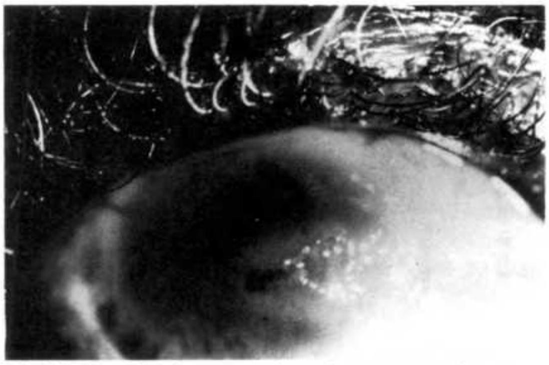
Fig. 3 *Case 3, right eye, two days after extracapsular cataract extraction. LK stage 4 is still present.*

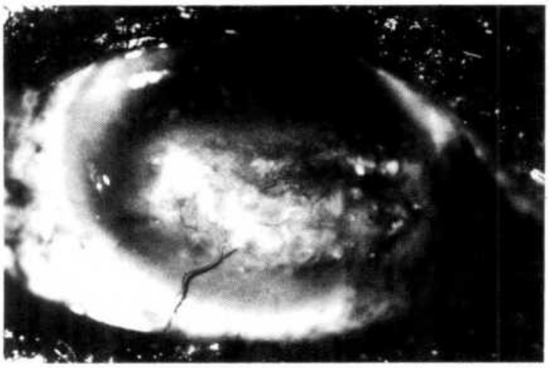

Fig. 4 *Case 7, right eye. LK stage 5 showing densely packed nodules with vascularisation due to recurrent infections.*

performed with the posterior capsule always being left intact. In LK stages 4 and 5 it was difficult to see the anterior capsule, so a broad sector iridectomy was done. In two cases where visualisation was particularly difficult a secondary aspiration of residual lens material was performed two days after the first operation. In those patients who underwent bilateral cataract extraction the interval between the two operations was less than one week. The patients were discharged a week after surgery with topical medication of Maxitrol drops (neomycin, polymgxin B, dexamethasone) four times a day for six weeks and atropine 1% drops twice daily for three months. The patients were supplied with non-tinted aphakic spectacles and returned for follow-up at two weeks and thereafter monthly for a minimum period of six months. At each visit anterior segment photographs of the eyes were taken, and staging of the LK was recorded following the criteria listed above. During the follow-up period there was no access to the preoperative staging. At the end of the clinical study the three authors relied on the photographs to confirm the pattern of the regression of the LK.

Results

Table 2 shows the results. There were 17 patients (26 eyes) who underwent extracapsular cataract extraction. Of these, nine patients (18 eyes) had bilateral cataract extraction. Twenty four eyes out of 26 (92%) showed regression of the LK following extracapsular cataract extraction. Table 3 shows the regression pattern of each stage postoperatively. The majority of cases improved to stage 2, in which only superficial corneal scars are left and visual acuity is markedly improved. These results show that there was a significant improvement in the corneal condition

Table 2 *Staging of LK pre- and postcataract extraction*

Case	*Eye (R, L)*	*Age (years)*	*Sex*		*Preoperative VAC staging*	*Postoperative VAC staging*	*Follow-up (months)*
			Male	*Female*			
1	L	58	M		LP 4	6/18 2	9
2	R	74	M		3/60 3	6/18 2	6
3	R	65	M		2/60 4 (fig. 2)	6/18 2 (fig. 5)	10
	L				LP 4	6/18 2	10
4	R	64	F		6/60 2	6/12 2	6
	L				6/60 2	6/12 2	6
5	R	70	M		LP 3	6/24 2	15
	L				1/60 3	6/18 2	15
6	R	75	M		LP 4	6/36 3	9
7	R	65	M		LP 5 (fig. 4)	1/60 4	10
	L				LP 5	3/60 4	10
8	L	61	M		6/60 3	6/18 2	14
9	R	58	M		3/60 3	6/12 2	6
	L				LP 3	6/18 2	6
10	R	70	M		6/60 2	6/9 1	6
	L				LP 4	6/36 3	6
11	R	71	M		LP 3	6/18 2	6
	L				6/60 3	6/18 2	6
12	R	76	M		HM 5	3/60 4	7
	L				LP 5	2/60 4	7
13	R	69	M		3/60 4	6/36 3	14
	L				6/60 3	6/24 3	14
14	R	65	M		2/60 4	6/36 3	7
15	L	68	M		LP 5	6/60 3	9
16	L	62	M		LP 4	6/36 3	6
17	R	74	M		1/60 3 (fig. 1)	6/9 1 (fig. 6)	6

VAC=visual acuity with correction. LP=light perception. HM=hand movements.

Table 3 *Distribution of postoperative staging of LK*

Preoperative staging	*No. of eyes*	*Postoperative results*				
		Stage 1	*Stage 2*	*Stage 3*	*Stage 4*	*Stage 5*
Stage 1	—					
Stage 2	3	1	2	–	–	–
Stage 3	10	1	8	1	–	–
Stage 4	8	–	3	5	–	–
Stage 5	5	–	–	1	4	–

following extracapsular cataract extraction ($p<0{\cdot}01$).

Patients who had unilateral cataract extraction (Table 4) showed concomitant regression in the fellow eye in three out of six eyes (cases 1, 16, and 17). Two eyes were phthisical and could not be assessed and three eyes (cases 6, 8 and 14) showed no alteration.

Discussion

Previous papers on LK have dealt mainly with its clinical description, epidemiology, incidence, aetiology, and histopathology. Very little is known about the treatment of this condition. Therapeutic measures recommended for LK include sunglasses, ocular lubricants, superficial keratectomy, and lamellar keratoplasty in advanced cases.[3] However, there have been no detailed reports on these therapeutic measures. So far the condition has been thought to be progressive or stationary.[5] There have been no previous reports on the regression of LK.

The results of our prospective clinical study have demonstrated a regression of the LK following extracapsular cataract extraction. The regression became evident between eight weeks and four months postoperatively. The most dramatic improvement occurred in the patients at stages 3 and 4, who regressed to stage 2 with marked improvement in visual acuity (Tables 2 and 4). Patients with stage 5 regressed generally minimally and those with stage 2 either remained the same postoperatively (case 4) or regressed to stage 1 (case 10). Therefore the regression of LK at the ends of the spectrum of the disease was less spectacular, both in eyes operated upon and those not operated upon.

Table 4 *Staging of LK in the unoperated eye pre- and postcataract extraction in the fellow eye*

Case	*Eye (R, L)*	*Condition of the unoperated eye*	*Preoperative VAC staging*	*Postoperative VAC staging*
1	R	Dislocated lens	LP 4	6/60 2
2	L	Phthisical eye	– –	– –
6	L	Incipient cataract	6/24 2	6/24 2
8	R	Incipient cataract	6/24 2	6/24 2
14	L	Aphakic	6/36 2	6/36 2
15	R	Phthisical	– –	– –
16	R	Incipient cataract	6/60 4	6/24 2
17	L	Incipient cataract	6/36 3	6/24 1

VAC=visual acuity with correction. LP=light perception.

The improvement in LK could have been due to a number of factors. Reduction in exposure to sunlight is important, since the relation between LK and exposure to ultraviolet irradiation is well documented.[3-6] Most of the patients in our clinical study came from the Northern Transvaal, in which the average annual duration of sunshine expressed as a percentage of possible sunshine is 80%. They were all edlerly, and their occpation and lifestyle had resulted in chronic exposure to solar irradiation. Aphakic photophobia is a well known phenomenon attributable to the absence of the lens, which absorbs 80% of the ultraviolet light. Glare disability in aphakes has been documented,[10 11] and the presence of a posterior capsule might aggravate it.[11]

Postoperatively most of our patients complained of

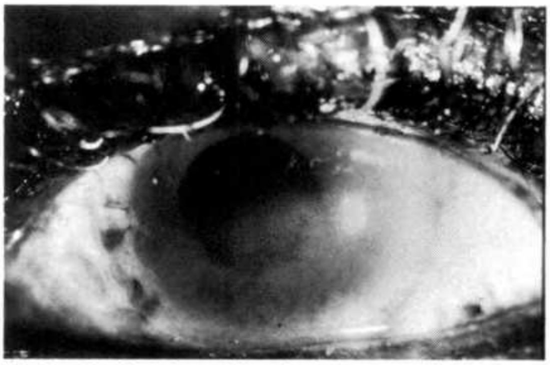
Fig. 5 *Case 3, right eye 12 weeks postoperatively. Note regression of the LK to stage 2 with residual superficial corneal scarring.*

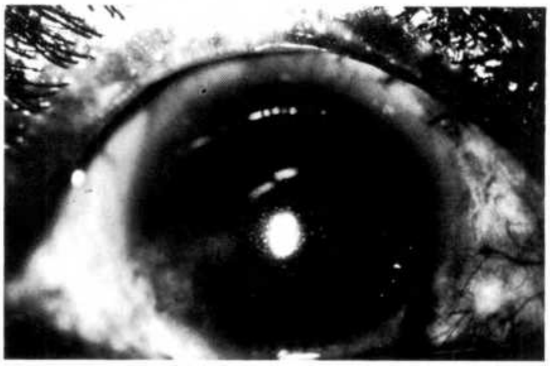
Fig. 6 *Case 17, right eye eight weeks after extracapsular cataract extraction. The nodules have disappeared leaving superficial stromal scarring, LK stage 1.*

photophobia which was enhanced by the use of atropine drops and non-tinted aphakic spectacles. They also reported spending less time outdoors since their operation. The cases listed in Table 4 underwent unilateral cataract extraction, and three out of six showed concomitant regression of the LK in the fellow eye. The unoperated eyes which did not show improvement in the LK belonged to stage 2. Operated eyes of stage 2 severity preoperatively also showed minimal improvement (Tables 2, 4). The unoperated eye was not treated with any topical medication; therefore the regression of LK could not be attributed to the postoperative treatment. Since the LK regressed several weeks after the patients were discharged, hospital diet could not be the cause. The diminished oxygen requirement of an aphakic eye should be considered as a possible factor in corneal change, but the concomitant regression in the unoperated eye would remain unexplained. Another possible mechanism which could explain the regression of LK is that, following extracapsular cataract extraction, some humoral immune factors are released and influence the pathophysiology of LK. This hypothesis would need further immunological investigations.

We performed extracapsular cataract extraction because it is our preferred technique for uncomplicated senile cataracts. Whether intracapsular cataract extraction will produce the same effect will be a subject of further studies. Temporary tarsorrhaphy was considered but seemed impracticable, since LK regresses only after eight weeks of protection of the cornea. Before our observations cataract surgery was not considered beneficial for patients with moderate to severe LK, because the corneal condition was believed to be stationary or progressive, therefore improvement in visual acuity was not expected. However, our study shows that in the presence of LK and mature cataracts, lens extraction is recommended.

The LK, if not in the advanced stage 5, may regress after eight weeks of reduced exposure to UV light. This occurs after cataract extraction because these patients, under atropine, are photophobic and avoid their usual exposure to sunlight.

We are indebted to Dr P J M Bucher, from the Ophthalmology Department, Elim Hospital, in the Northern Transvaal, for his valuable collaboration in this clinical study.

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Warburg (HARD±E) syndrome without retinal dysplasia: case report and review

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SUMMARY Warburg syndrome is a recently defined autosomal recessive oculocerebral syndrome. It was previously given the acronym HARD±E, indicating what were regarded as the pathognomonic features, namely hydrocephalus, agyria, and retinal dysplasia with or without encephalocele. We report the case of a male infant with the typical cerebral features of hydrocephalus, agyria, and pseudoencephalocele, but without retinal dysplasia. Peters' anomaly and optic nerve hypoplasia were the main ocular defects. We believe that anterior chamber defects and optic nerve hypoplasia are the ocular defects more directly related developmentally to the cerebral defects. Definition of ocular defects is important, since diagnosis and counselling rely heavily on ocular signs, which help to distinguish this syndrome from neural tube defects in general.

Congenital cerebral abnormalities were reported to be associated with a variety of eye defects. In the absence of polydactyly and polycystic kidneys, which characterise the Meckel syndrome,[1] the association of hydrocephalus, agyria, and in some cases encephalocele with retinal dysplasia was recognised as a specific syndrome and was given the mnemonic HARD±E syndrome by Pagon *et al.*[2] More recent reports and reviews[3-5] have emphasised the variability of expression of this autosomal recessive disorder. Pagon *et al.*[3] suggested that the eponym Warburg syndrome be used instead of HARD±E.

We report a case with typical cerebral features of Warburg syndrome but without retinal dysplasia.

Case report

A full-term white male baby was born to young Caucasian unrelated parents. The pregnancy was normal, with no history of maternal disease or drug intake. Previous obstetric history included a spontaneous abortion at 10–12 weeks and the birth of a normal female infant. No family history of any congenital abnormality could be elicited. Birth weight was 2960 g, length 48 cm, and head circumference 33·7 cm. External examination (Figs. 1, 2) showed micrognathia, hypertelorism, low-set ears, and a cleft palate extending to the gingival margin. The occipital region showed a reducible, non-pulsatile protrusion, overlying a small bony defect. The overlying skin showed a tuft of hair, covering a dermal sinus. A head scan revealed grossly dilated lateral and third ventricles and absent corpus callosum. A body scan showed the right kidney to be enlarged, with large cystic spaces. Both eyes were enlarged and protuberant, with increased corneal diameter to 13 mm each. There were localised central corneal opacities, denser in the left than in the right cornea (Fig. 1). The pupils were small and fixed, with a transverse diameter of 2·9 mm (right) and 1·7 mm (left). The irides appeared stretched and slightly atrophic. The intraocular pressure was raised to 26 mmHg (right) and 28 mmHg (left), as measured with a Perkins applanation tonometer. A faint red reflex was evident in both eyes. There was no obvious nystagmus or strabismus. Chromosomal analysis revealed a normal male karyotype. Serology titres for herpes simplex, rubella, and cytomegalovirus were not increased. The infant died at the age of 4 days.

Post-mortem examination confirmed the facial anomalies. Other abnormalitities were confined to the eyes, brain, and urinary system. There was a

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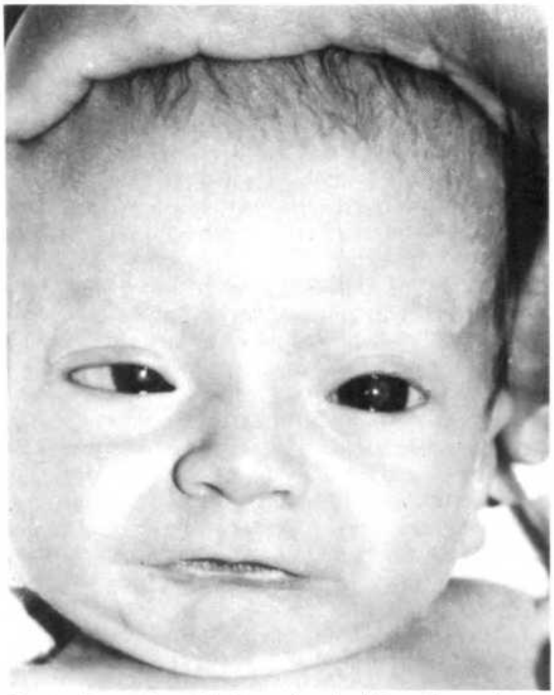

Fig. 1 *Front view of the face, showing bilateral central corneal opacities.*

marked right hydronephrosis and hydroureter, caused by a stricture of the distal end of the ureter. The left kidney showed multiple nodules of focal renal dysplasia in the upper pole.

OCULAR PATHOLOGY

Shortly after death both eyes were examined under the biomicroscope. The right eye (Fig. 3) showed a faint central corneal stromal opacity and a posterior central stromal defect, consistent with Peters' anomaly. The anterior chamber was very shallow at the periphery and absent centrally, with apparent adhesions of the iris-lens diaphragm to the posterior surface of the cornea, at the pupillary area. The left eye showed a denser central corneal stromal opacity. Neither corneal stromal defect nor central adhesions between the cornea and iris-lens diaphragm could be detected. The anterior chamber was also very shallow.

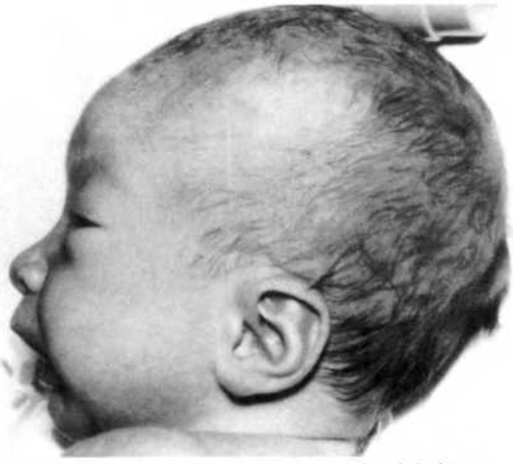

Fig. 2 *Lateral view of the head, showing buphthalmos, micrognathia, low-set ear, and pseudoencephalocele.*

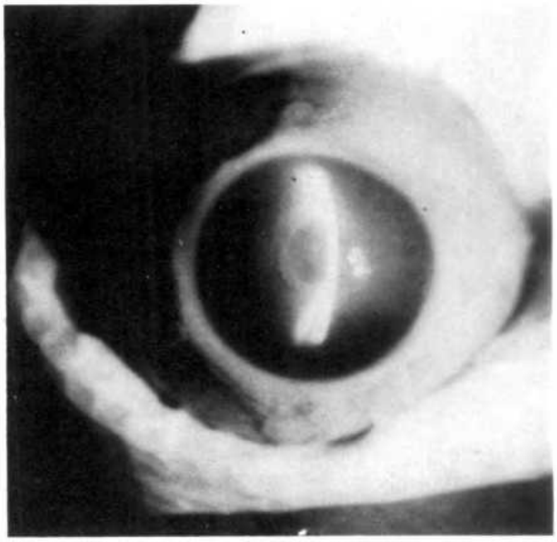

Fig. 3 *The right eye, as seen through the biomicroscope. Note the central corneal stromal opacity, central posterior corneal defect, and very shallow anterior chamber, which is obliterated centrally.*

Examination of the fixed specimens showed both eyes to be enlarged (diameters right and left: 21 mm transverse, 19 mm anteroposterior, and 20 mm superoinferior). On cross section each eye showed an optic disc, an optic nerve stump, and retinal blood vessel of normal appearance. Both retinae were attached, with no folds or colobomata. A thin, translucent, non-vascular band extended from the optic disc to the posterior surface of the lens in each eye.

Microscopic examination of the right eye (Fig. 4) confirmed the central corneal defect involving the posterior stroma, with complete absence of the endothelial cell layer and Descemet's membrane over the defect. The pupillary margin of the iris showed evidence of adhesion to the margins of the central corneal defect, with no inflammatory cellular infiltrate detected. The left eye (Fig. 5) showed no central corneal defect apart from a rather thin Descemet's membrane. The iridocorneal angle was

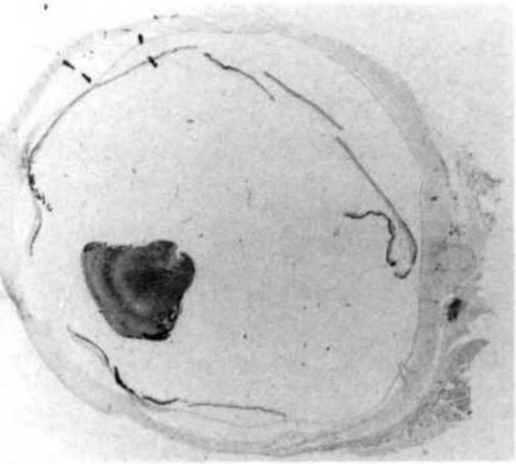

Fig. 4 *Cross section of the right eye. Note the posterior central corneal defect, posterior lenticonus, and normal appearance of the retina. (H and E, ×3).*

normal and open bilaterally, with a normal trabecular meshwork and canal of Schlemm. The lens capsule was intact in both eyes. There was a right posterior lenticonus and central lenticular calcification (Fig. 4) and a left posterior cortical cataract. Both retinae showed a normal layering with a normal retinal pigment epithelium. Retinal ganglion cells could be detected in their normal place but were diminished in number. There was no evidence of rosette formation in either retina when multiple sections were studied. Optic discs were confirmed bilaterally by the absence of overlying retinal tissue. The lamina cribrosa showed no evidence of cupping. Both optic nerve stumps were of normal size. They were formed mainly of glial cells and failed to show the staining reactions either for nerve fibres (axons) or for myelin.

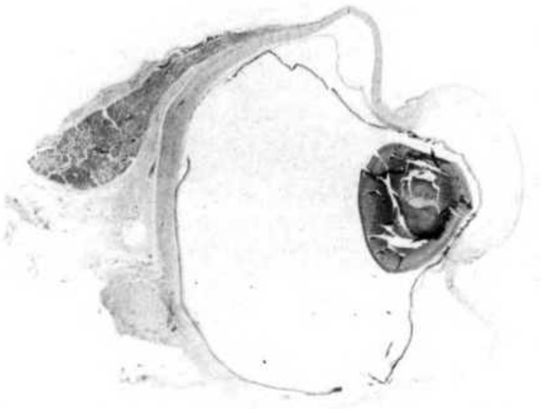

Fig. 5 *Cross section of the left eye. Note the thick cornea, the thin sclera, and the normal appearance of the retina. (H and E, ×2·7).*

NEUROPATHOLOGICAL FINDINGS

The skull was large. The dura mater was normal, but the falx cerebri was very short. The cerebrum showed total agyria, with the longitudinal and Sylvian fissures only slightly formed. Olfactory bulbs and tracts, optic nerves, chiasma, optic tracts, and lateral geniculate bodies were not identified. Coronal section of the cerebrum (Fig. 6) showed gross hydrocephalus and a continuous ventricular cavity, due to the absence of septum pellucidum and roof of the third ventricle. The basal ganglia, thalamus, and hypothalamic structures were seen only as a bilateral mass of grey matter. In most places the cerebral cortex and white matter were reduced to a thin strip, which on histological examination showed a cortex formed by neurons lacking the orderly, layered arrangement, and a very sparsely myelinated white matter containing islands of migrating neuroblasts. The corpus callosum was severely hypoplastic and visible only as a nodular ridge. In the posterior fossa a Dandy-Walker malformation was identified which had caused distortion of the cerebellar hemispheres and brain stem and widening of the floor of the fourth ventricle. The cerebellar vermis showed hypoplasia and severe cortical dysplasia. The cerebellar hemispheres showed a moderate cortical dysplasia. The cerebellar nuclei and the nuclei of the brain stem were identified, and the cranial nerves emerging from the brain stem and their nuclei were normal.

The aqueduct of Sylvius was also normal. The bulging of the scalp over the small occipital defect was due to a pseudoencephalocele, since there was no histological evidence of its continuity with the cranial cavity or the presence of meningeal or neuroglial tissue.

Discussion

The acronym HARD±E was applied to cases showing hydrocephalus, agyria, and retinal dysplasia with or without encephalocele, based on early reports.[2 6-8] The cases reported by Warburg[9] were also suspected of being related but were not included owing to insufficient evidence. Pagon *et al.*,[3] Bordarier *et al.*,[4] and Whitley *et al.*[5] have redefined the syndrome in the light of recent reports. They considered that a less restrictive name than HARD±E was necessary. The suggestion of Pagon *et al.*[3] to call it Warburg syndrome was accepted in recognition of the pioneer work of this researcher.[10]

Retinal dysplasia and non-attachment were found in almost all of the eyes studied histologically. In the present case, however, both retinae were normally

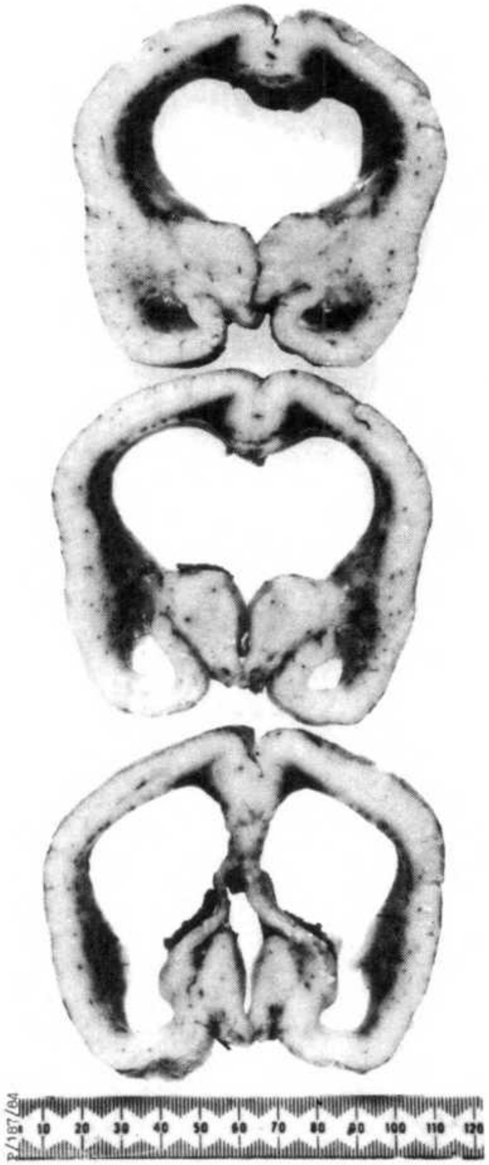

Fig. 6 *Coronal sections of the cerebrum, showing agyria, hydrocephalus with a large single ventricular cavity, and absence of optic nerves and chiasma.*

attached. No rosette formation could be detected to indicate retinal dysplasia. Lahav and Albert[11] postulated that retinal dysplasia is caused by cellular proliferation of the inner layer of the optic cup, which may be accompanied by folding of the retina. This can occur as an abortive response of a retina, damaged by a number of factors, such as viral infection. They also suggested that orderly retinal development may depend on the organising influence of an adjacent retinal pigment epithelium. Hence non-inflammatory retinal dysplasia usually develops over areas devoid of pigment epithelium and in congenitally non-attached areas. This indicates that retinal dysplasia is secondary to retinal non-attachment during a faulty development of the optic vesicle. As it is a common, non-specific, and non-pathognomonic abnormality,[11] it is not appropriate to consider retinal dysplasia a primary major component of the Warburg syndrome.

The ocular signs of Warburg syndrome have been listed in recent reviews.[3-5] They included different degrees of Peters' anomaly, unilateral and bilateral.

There were also cases with a combination of central and peripheral anterior chamber defects[3 8] and cases with peripheral defects only.[3] In the cases with Peters' anomaly central corneal opacity was the commonest sign. Other opacities in the media were also common, namely, congenital cataract and persistent hyperplastic primary vitreous. A degree of both was found in the case reported here. The posterior lenticonus seen in this case has also been previously reported.[12] When a clear view of the fundus could be achieved, a pale non-attached retina, together with retinal folds, would be the commonest sign expected. Optic disc hypoplasia and colobomata may also be seen. Abnormalities of the size of the globe were frequent, including microphthalmia and, less commonly, buphthalmos, as in the present case.

Bilateral optic nerve hypoplasia was prominent in the case reported here. It is believed to result from a failure of the retinal ganglion cells to form nerve fibres while the mesodermal component of the optic nerve develops, forming an optic disc and retinal blood vessels.[13-15]

Yanoff *et al.*[13] reported a case with striking similarities to our case, including agyria, hydrocephalus, cerebellar hypoplasia, clouded corneas, micrognathia, low-set ears, and unilateral hydronephrosis. Retinal dysplasia was also not detected. The main ocular feature in that case was bilateral optic nerve aplasia, the pathogenesis of which is believed to be similar to that of optic nerve hypoplasia.[14] The absence of the mesodermal component recognised by the absence of optic discs and retinal blood vessels is probably due to lack of induction caused by the absence of nerve fibres.[13 14]

In the case reported here the possibility of optic nerve atrophy secondary to glaucoma rather than primary hypoplasia could be excluded, as the intraocular pressure was only slightly raised, and that was mainly compensated for by enlargement of the globes, with no definite cupping of the optic discs.[16]

The posterior corneal defect in Peters' anomaly could be explained by an incomplete migration of the initial two waves of mesenchymal cells, which form the corneal endothelium with its Descemet's membrane and then the corneal stroma.[17 18]

Johnston[19] concluded that the cephalic neural crest provides the origin for most facial and ocular structures apart from the retina and lens, epithelial tissues, vascular endothelia, and skeletal muscle cells. He suggested that the neural crest cells, forming the mesenchyme of the frontonasal processes, are derived from the forebrain neural folds and that the formation of the neural tube and crest may depend on the same inductor. Inadequate induction could result in simultaneous deficiencies of both structures. The frontonasal crest must form a relatively large mass of cells in a limited time to achieve normal primary palate formation. Experimentally, reducing the number of these crest cells in the chick and mouse embryos resulted in cleft palate with associated brain and eye defects.

Bahn *et al.*[20] introduced a classification of corneal endothelial disorders based on neural crest origin. They postulated that Peters' anomaly, together with other anterior chamber cleavage syndrome variants and congenital glaucoma, is caused by an abnormal neural crest cell migration.

The present case shows a combination of cleft palate, Peters' anomaly, and a deficiency of forebrain tissue including the cerebral cortex, diencephalon and sensory retina, which shows a deficiency of retinal ganglion cells causing optic nerve hypoplasia. All these defects could be caused by a developmental failure of the forebrain and its associated neural crest. Optic nerve hypoplasia, together with Peters' anomaly and other anterior chamber defects, could be considered the ocular abnormalities more directly related developmentally to the brain defects in Warburg syndrome.

Three associated anomalies in the case reported here are worthy of comment. Micrognathia was reported in three other cases[4 13] and unilateral hydronephrosis in one case.[13] Cleft palate was not reported in the literature but has been noted in another case (P Farndon, unpublished observation).

Warburg syndrome is regarded as being an autosomal recessive trait. This is supported by its frequent occurrence in sibs,[3 4 7 12 21] the consanguinity of parents in one family,[7] the good health of all the parents involved, and the lack of evidence of any other aetiology, such as maternal infection or drug intake. The diagnosis of Warburg syndrome is important so that the parents can be advised of its 25% recurrence risk and of the possibility of prenatal diagnosis by detailed ultrasound study. The ocular signs are the major clues to the clinical diagnosis of Warburg syndrome in a neonate with a major neurological deficit and a demonstrable hydrocephalus with or without a posterior encephalocele.

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Sussex Eye Hospital sports injuries

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SUMMARY To assess the prevalence of sports eye injuries in our area a register was kept over the 18 months from October 1982 to March 1984. Squash, association football, badminton, and tennis were the main offenders. The severest injury was from a golf ball, involving a fractured zygoma. There was one retinal dialysis, and one lens dislocation requiring extraction. Spectacles were broken in six cases and a contact lens in one. Glass fragments needed operative removal in one case, but there were no penetrating injuries. The value of eye protection, not worn by any of our patients, is emphasised.

Despite the assurance of a past president of the Wimbledon Squash and Badminton Club that 'badminton and squash are low in the table of eye injuries',[1] such accidents are on the increase. We were interested to estimate the ocular morbidity from these and other sports. The value of certain eye guards has been established in several sports, and our data strongly support their use. No doubt the decision to wear eye protection should remain with the individual, but we consider the dangers of sport should be more fully appreciated by the public.

Material and methods

All sports injuries presenting to the Sussex Eye Hospital between 1 October 1982 and 31 March 1984 were entered in a register. Three outpatient notes were untraceable, but the register showed these to be minor injuries only. Hospital notes were available for all other cases and our data are derived from these.

Results

Table 1 summarises the numbers and percentages of patients in various groups. As expected from previous reports,[2] squash was responsible for the most casualties. However, soccer and badminton each produced more admissions to hospital (soccer 7, badminton 4, squash 3). When combined, soccer and rugby football produced more casualties than squash (combined football 25, squash 24). Combining squash with other racket sports restores the lead (combined rackets 51, combined football 25).

Seventeen patients (18·3%) were admitted to hospital. Criteria for admission cannot be precisely defined, but the commonest indication was macroscopic hyphaema, as a precaution against secondary haemorrhage. Thus 16 of the 20 cases of macroscopic hyphaema were admitted, and only one admission did not have a macroscopic hyphaema.

Initial loss of visual acuity was scored as the number of line difference between the two eyes on the Snellen chart. We then extrapolated beyond 6/60 by adding one line for counting fingers, two for hand movements, and three for perception of light only. This is a questionable statistical manoeuvre, but seems reasonably consistent within this survey and has been used before.[3] The mean number of lines lost per patient was calculated for each sport. Golf scored the highest figure (5·5), but only two players were involved. Badminton and soccer were also higher scorers than squash (badminton 2·43, soccer 2·05, squash 1·65). Visual recovery was generally good: in only three cases was the last recorded acuity more than two lines worse than the other eye. One tennis player was known to be amblyopic in the injured eye. His acuity loss was scored as zero. Amblyopia was also suspected in two sportsmen who saw worse with their uninjured eyes. Their acuity loss was also scored as zero.

Of our patients 75·3% were male, presumably reflecting greater participation by males than females rather than greater male accident-proneness. The sports in which women predominated were badmin-

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Table 1 *Distribution of patients in categories according to sport*

	Squ	*Soc*	*Bad*	*Ten*	*Rug*	*Cri*	*Bas*	*Hoc*	*Gol*	*Mar*	*Kar.*	*Lax*	*Total*	*Percent*
Total	24	19	16	11	6	5	3	3	2	1	1	1	92	100
Admit	3	7	4	1	0	0	0	0	1	1	0	0	17	18·5
Not	21	12	12	10	6	5	3	3	1	0	1	1	75	81·5
Male	18	19	6	9	6	4	1	2	2	1	1	0	69	75·0
Female	6	0	10	2	0	1	2	1	0	0	0	1	23	25·0
Ball	17	15	11	11	1	5	1	2	2	1	—	0	66	72·5
Bat	5	4	5	0	5	0	2	1	0	0	—	1	23	25·3
Unknown*	2	0	0	0	0	0	0	0	0	0	0	0	2	2·2
Av. Age	31	25	37	30	25	23	14	16	32	13	27	?	28·5	—
In. Ac. Loss	1·65	2·05	2·43	1·09	1·33	1·20	0·00	0·67	5·50	1·00	0·00	0·00	1·71 (mean)	—
Hyphaema	3	6	7	1	1	0	0	0	1	1	0	0	20	21·7
H. Admit	3	6	4	1	0	0	0	0	1	1	0	0	16	(80·0)
Ret. Abn.	4	8	0	3	1	0	0	0	1	0	0	0	17	18·5

Sports Squ=Squash. Soc=Association football. Bad=Badminton. Ten=Tennis. Rug=Rugby football. Cri=Cricket. Bas=Basketball. Hoc=Hockey. Gol=Golf. Mar=Marbles. Kar=Karate. Lax=Lacrosse.
Categories Admit=number admitted. Not=number not admitted. Ball=number struck by ball. Bat=number struck by other agent. Av. Age=average age of patients. In. Ac. Loss=Initial average acuity loss. Hyphaema=number with hyphaema. H. Admit=number admitted with hyphaema. Ret. Abn=Retinal abnormality.
*Excludes the one karate player.

ton (10F, 6M), basketball (2F, 1M), and lacrosse (1F, 0M).

All but one of the 13 sports were ball games, the exception being karate. In the ball games 65 patients were hurt by the ball. The other 27 patients were mostly injured by the appropriate implement, but bodily contact was sometimes responsible, notably in rugby football, where the ball caused only one of the six injuries.

Perhaps surprisingly, the oldest casualties were not golfers but badminton players, with squash casualties the third oldest. Possibly the risk of injury in the more active sports increases with age. The oldest casualty was a 72-year-old male badminton player, the youngest a 9-year-old male footballer. Seventeen casualties were children under 16.

Of the retinal abnormalities oedema was the commonest finding, usually at the posterior pole. Footballers were most often affected (8/19 cases). Haemorrhage was noted in seven cases, entering the vitreous in two. There were two cases of choroidal rupture, and one of retinal dialysis which required plombage.

Broken glass was confined to squash players (two spectacles broken) and badminton (four spectacles and one contact lens broken). One of the squash players needed operative removal of glass fragments from his cornea and conjunctiva, but there were no penetrating injuries. One badminton player still has glass in his cornea and sees 6/9 with that eye, 6/6 with the other. There were two cases of diplopia, associated with a fourth nerve palsy in the karate player and a fractured zygoma in a golfer. Both failed to attend for review.

Discussion

With increasing leisure, sport has become more popular and sports injuries more frequent. In Glasgow in 1923 only seven out of 1000 eye injuries treated as 'indoor patients' were adult sports injuries.[4] In Northern Ireland in 1976 the equivalent figure was 84 out of 2032 admissions.[5] Recently in Bristol 2·5% of all cases of casualty eye trauma were caused by sport.[6] Our figure over 18 months was 0·58%. More alarmingly, in Massachussetts from 1960 to 1980, 3% of all enucleations followed sports injuries, though about half of these involved airguns, which are less popular in Great Britain.[7] In 1978 in the United States it was reported that 12% of all eye injuries were related to sport and recreation equipment, and that the number of injuries from the 10 most hazardous sports had increased by 58% over the preceding five years.[8]

The intrinsic risk of six sports, in terms of the number of eye injuries per 100 000 playing sessions, has been estimated from data obtained in the 1977 General Household Survey.[2] Squash was the most dangerous sport, and also carried the highest rate of admission per injury. Our experience is that, while squash produced most casualties, severer injuries resulted from golf, badminton, and football. Neither here nor in Southampton did any squash player suffer long term visual loss, but in Malaysia, where 63 eye injuries from badminton were recorded over five years, 36·5% of injured eyes ultimately saw only 6/12 or worse.[9]

The efficacy of suitable eye protection has been confirmed in the field and in the laboratory. Since

1977 in the United States eye protection has been mandatory for high school and college ice hockey.[8] An estimated saving of 70 000 eye injuries and $10 000 000 annually has resulted.[10] Similar Canadian legislation produced a fall in reported eye injuries from 253 to 90 in a two-year period.[11] In the laboratory, Fiegelman fired racquet balls at 65 miles per hour (105 km/h) at a variety of eye guards mounted on a model head fitted with a pressure transducer as an eye.[12] (A racquetball is larger and softer than a squashball.) All open (lensless) guards failed, being either penetrated or displaced. All spectacles, glass or plastic, failed because the lens or frame shattered. Only polycarbonate plastic safety lenses never shattered, and Fiegelman recommends this material for frames as well as lenses. No lensless guard passed American or Canadian safety tests,[13] and such guards may give a false sense of security, encouraging dangerous play.[14]

A drop-ball test confirmed the general belief that minus lenses are more fragile than plus ones, though not where central thickness is equal.[15] This is important, as nearly all sportsmen who wear glasses are myopes, the hypermetropes generally being young enough to accommodate for sport without correction. Thus in Ingram and Lewkonia's series of 21 squash eye injuries all eight spectacle wearers were myopes, and all four penetrating injuries were in spectacle wearers.[16] It must be emphasised that standard spectacles or contact lenses offer no protection in these sports, but greatly increase the chance of penetrating injury. Moreover the impression that experience reduces the likelihood of injury is not supported by the evidence.[17–19]

Effective eye guards are not easily obtained in our area. Inquiries at all the main Brighton sports shops found only two selling such guards, and these were the lensless variety. Only one or two are sold per month, and always to people who have already been injured. Unfortunately, of our two patients making their second visits with sports eye injuries, neither had got around to buying a guard. We did eventually discover one optician in Brighton who knew where to obtain polycarbonate guards, but there was insufficient demand to stock them.

Seatbelt legislation has survived initial unpopularity to reduce traffic related eye injuries by an estimated 75%.[20] It is time pressure was brought to bear on the ever increasing number of sportsmen to save themselves unnecessary eye damage. First class cricket has begun to make protection acceptable in this country, and other sports should follow its lead. An editorial in the *British Medical Journal* in 1973 chose to continue playing squash 'naked eye', but hoped an efficient eye hospital would be accessible.[21] This position should be reconsidered. Eye protection for dangerous sports should be the norm, not the exception.

The help and encouragement of Mr A F Harden are gratefully acknowledged.

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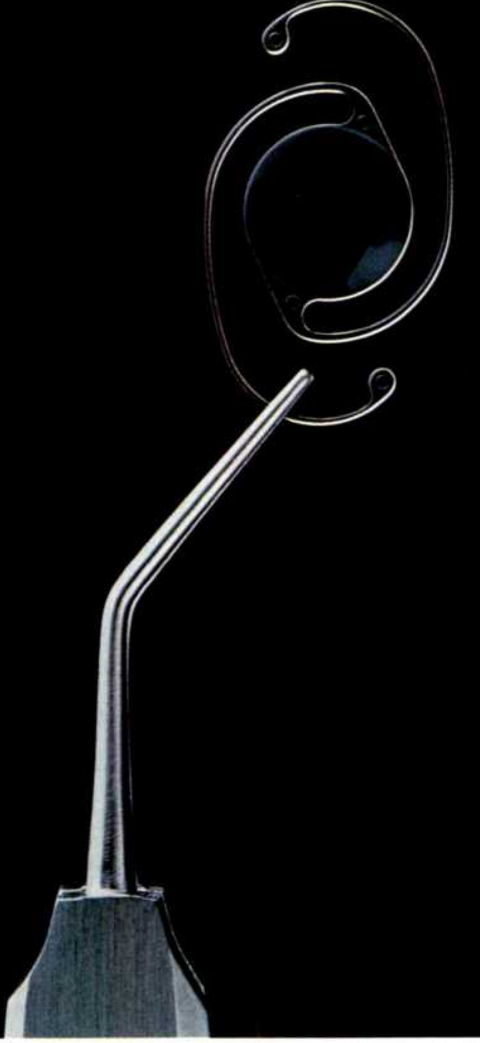

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Cryopreservation of rabbit corneas: assessment by microscopy and transplantation

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SUMMARY Rabbit corneas were frozen and thawed by three methods and compared by full thickness transplantation as well as specular microscopy, histology, and transmission electron microscopy. Two of the methods used a recently described technique, in which the excised cornea was immersed in a potassium-rich buffered solution containing the cryoprotectant dimethyl sulphoxide (Me$_2$SO, 2 mol/l). This solution was designed to restrict the loss of intracellular potassium and to prevent cell swelling at low temperatures. In one group the corneas were frozen and thawed surrounded by 5 ml of medium, while in the second group corneas were drained of excess fluid and frozen in air. The third group consisted of corneas cryopreserved by Capella and colleagues' method. All the cryopreserved corneas were damaged, but those that had been frozen in air after exposure to the new medium showed better structure and function than corneas frozen by either of the other two techniques.

It has been reported that corneas cryopreserved by the methods of Mueller[1] and Capella *et al.*[2] are as effective in clinical transplantation as fresh nonfrozen material.[3,4] Nevertheless, neither method of corneal storage has gained general acceptance. Capella *et al.*[2] reported a high proportion of surviving endothelial cells when assessment was made by histochemical methods, and Van Horn *et al.* confirmed this finding using transmission and scanning electron microscopy.[5,6] However, the reliability of histochemical assays as predictors of viability may be questioned,[7] and more recent studies employing both electron and specular microscopy have shown grossly disorganised endothelium without barrier function.[8,9]

Mueller used a conventional balanced salt solution as a vehicle for the introduction and removal of the cryoprotectant dimethyl sulphoxide (Me$_2$SO), but Capella and colleagues employed a solution containing only sucrose and albumin in addition to Me$_2$SO. Corneas exposed to this medium have been shown to be severely dehydrated and to have lost significant amounts of sodium and potassium.[10] Disturbances of the ion and water content of tissues during preservation have been widely investigated. In one such study it was found that increasing the concentration of potassium and substituting a high molecular weight zwitterionic buffer for some of the chloride resulted in improved cryopreservation of smooth muscle tissue.[11,12] A similar solution has been proposed for cryopreservation of the cornea.[13,14] It contains the buffer N-tris (hydroxymethyl)-methyl-2-aminoethane sulphonic acid (TES) and is designated CPTES using two modes of storage. In the first, corneas were frozen, stored and thawed while sur-introduction and removal of 1 and 2 molar Me$_2$SO in this solution at 0°C.

In this paper we describe the cryopreservation of rabbit corneas after incubation in 2 molar Me$_2$SO in CPTES using two modes of storage. In the first, corneas were frozen, stored and thawed while surrounded by 5 ml of the 2 M.Me$_2$SO-CPTES medium; in the second method, following the work of Mueller[1] and Taylor *et al.*[8] corneas that had been permeated by the cryoprotectant were then drained and frozen surrounded by air. For comparison, a third group of rabbit corneas was cryopreserved by the technique of Capella *et al.*[2] Survival was assessed by light microscopy and transmission electron microscopy of corneas immediately after thawing and removal of the cryoprotectant, and by transplantation of full thickness corneal grafts. The grafts were evaluated by slit-lamp examination and in-vivo specular microscopy. After one week they were removed, corneal

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thickness was measured on the in-vitro specular microscope, and histological examination was carried out.

Materials and methods

PREPARATION OF CORNEAS

Corneas were obtained from New Zealand White rabbits (2–2·5 kg) that had been killed with pentobarbitone. The excised corneas were prepared by the method of Dikstein and Maurice[15] and were mounted on plastic support rings to prevent wrinkling and distortion. Control corneas were prepared by the same method but were placed in glutathione bicarbonate Ringer's solution,[8] gassed with 95% oxygen, 5% carbon dioxide (pH7·4) at 0°C, and transplanted without delay.

CRYOPRESERVATION PROCEDURE

CPTES method. Corneas were immersed endothelial side uppermost in 5 ml of 2 molar Me_2SO in CPTES solution at 0°C for 20 minutes; 25 ml polypropylene vials with screw caps were used for this purpose. CPTES contained (mmol/l) Na^+ (31), K^+ (100), Mg^{++} (0·78), Cl^- (30), HCO_3^- (30), $H_2PO_4^-$ (1), SO_4^{--} (0·78), glucose (5), TES (100). The pH was 7·7 at 25°C and the osmolality 301 mosmol/kg. Corneas that were to be frozen in air were then transferred to an empty vial but no attempt was made to remove the last traces of solution. The vials were placed in an alcohol bath thermostatically controlled at −10°C for 10 minutes, and freezing was initiated by touching the scleral rim or the immersion solution with a small ice crystal (seeding). Five minutes later the vials were transferred to a programme-controlled cooling apparatus set to cool at 1°C per minute to −70°C.[16] At this temperature the specimens were transferred to liquid nitrogen (−196°C) for storage. Thawing was carried out by immersing each vial in a 37°C water bath for 3–4 minutes, and removing it just before the last ice had melted. Corneas that had been frozen in air were immersed in 5 ml of 2 molar Me_2SO in CPTES at 0°C. All corneas were then transferred into 5 ml of 1 molar Me_2SO in CPTES, and, at intervals of 5 minutes, first 5 ml of CPTES and then 10 ml was added, producing a final Me_2SO concentration of 0·25 molar. After 5 minutes in this solution the corneas were transferred to 5 ml of rabbit serum at 0°C and allowed to warm to room temperature.

Capella and colleagues' method. The method used in this study was that described by Capella *et al.*[2] and is typical of the several related techniques described by these authors. According to this method the corneas were exposed to a series of solutions containing progressively increasing concentrations of Me_2SO and sucrose. The final solution contained 7·5% v/v Me_2SO (1 mol/l). The vials were transferred to an alcohol bath at −12°C, seeded, and cooled at 3°C per minute to −70°C. The vials were then transferred to liquid nitrogen for storage. The corneas were thawed by transferring the vials to a 37°C water bath, removing them before the last trace of ice had melted, and placing the corneas in 5 ml of rabbit serum at 0°C for 10 minutes. Each cornea was then transferred to a second 5 ml aliquot of rabbit serum at 0°C and allowed to warm to room temperature.

TRANSPLANTATION

Adult Dutch rabbits (2–3 kg) were anaesthetised by the intramuscular injection of fluanisone and fentanyl citrate (Hypnorm, Jansen 0·5 ml per kg) and intravenous pentobarbitone as required to achieve abolition of the foot withdrawal reflex. Two drops of 1% amethocaine were applied to the eye and 1000 units of heparin given intravenously. The pupil was widely dilated with 1% atropine, 1% cyclopentolate, and 10% phenylephrine drops. Periorbital hair was trimmed, and the globe was exposed and immobilised with two 4/0 sutures through the extraocular muscles. A 6 mm corneal button was trephined from the donor cornea on its plastic support ring, and transferred by means of two peripheral 10/0 nylon sutures to a recipient bed of the same diameter. One drop of 2% methylcellulose was placed on the lens surface to prevent the protuberant lens touching the endothelium. Four temporary interrupted 10/0 nylon sutures secured the graft in position while a continuous 10/0 nylon suture was placed. The anterior chamber was allowed to reform spontaneously, and chloramphenicol and atropine ointments were applied at the end of the procedure. Grafts were performed with corneas from the three experimental groups in random order. The animals were examined by slit-lamp biomicroscopy daily. The only postoperative care required was occasional atropine drops when the pupil was miotic.

METHODS OF ASSESSMENT

Electron microscopy. Freshly thawed corneas, still mounted on their support rings, were fixed in 3% glutaraldehyde in 0·15 molar cacodylate buffer (pH 7·2, osmolality 305 mosmolal before addition of glutaraldehyde). After 24 hours of fixation at room temperature the corneas were removed from the rings, diced, and postfixed in 1% osmium tetroxide in cacodylate buffer for 1 hour followed by 1% aqueous uranyl acetate. The specimens were dehydrated in an alcohol series and embedded in Araldite. The sections were cut on an LKB Ultratome 1, stained sequentially with uranyl acetate and lead citrate, and viewed in a Zeiss EM9S2B electron microscope.

Light microscopy. Corneas were fixed in 10%

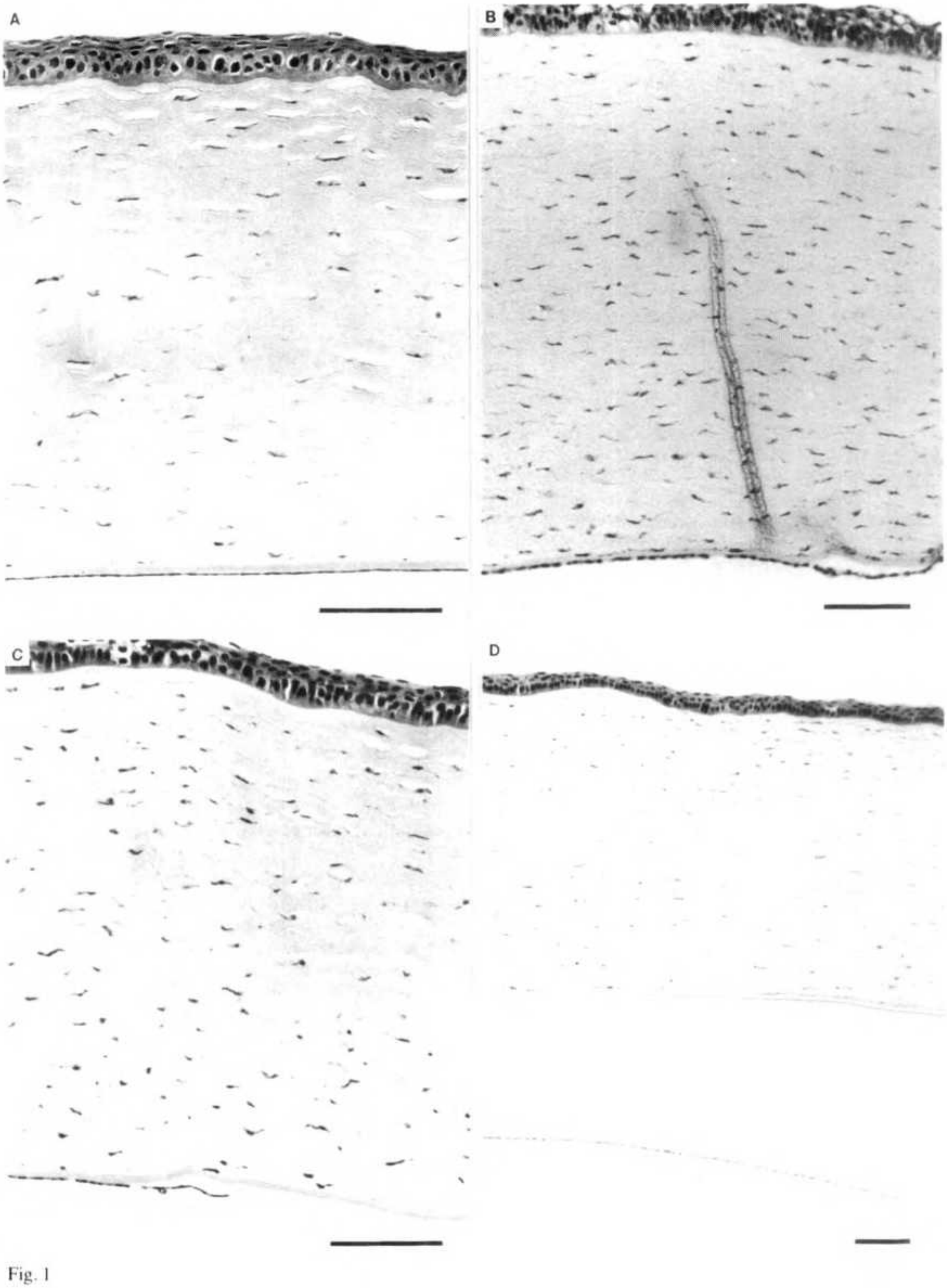

Fig. 1

formol saline, dehydrated in alcohol, embedded in paraffin wax, sectioned, and stained with haematoxylin and eosin.

Specular microscopy. In-vivo specular microscopy was carried out on the fifth and seventh postoperative days. The microscope was a prototype model; it had a ×40 applanating cone lens and was fitted to a Haag-Streit slit-lamp base. On the seventh postoperative day each animal was killed and the freshly enucleated eye was examined by in-vitro specular microscopy.[8] The epithelial surface was covered with silicone oil to prevent evaporation and to provide an immersion medium for the objective lens. After measurement of corneal thickness the tissue was processed for histology.

Results

OBSERVATIONS ON CORNEAS IMMEDIATELY AFTER THAWING

HISTOLOGY (5 corneas from each experimental group)

The normal histology of the cornea is shown in Fig. 1A. In all experimental groups the endothelial monolayer was to a considerable extent detached from Descemet's membrane (Fig. 1B–D), but lateral cell-to-cell adhesion was well maintained. A layer of amorphous eosinophilic material was observed between the endothelium and its basement membrane (Fig. 2). Many of the cells appeared degenerate, with disrupted, vacuolated cytoplasm and pyknotic nuclei. The stroma was thickened but keratocytes appeared normal. Epithelium was irregular in thickness and many of the cells were vacuolated. There were no clear distinguishing features between the three experimental groups.

ELECTRON MICROSCOPY (1 cornea from each experimental group)

Five areas were examined in each cornea. The endothelium of corneas frozen by each method exhibited variable, and in some cases severe degrees of structural damage (Fig. 3A–D). Nuclear changes ranged from slight margination of chromatin to complete karyolysis. Mitochondrial changes ranged from slight swelling of the outer compartment, through vesicle formation of the inner mitochondrial membrane and pallor of the matrix, to gross swelling of the inner compartment and degeneration of the inner mitochondrial membrane. Except in severely disrupted cells the rough endoplasmic reticulum showed only moderate dilatation of the cisternae with no loss of matrix density.

The endothelium showed varying degrees of detachment from Descemet's membrane. Least damage was observed when the cornea had been frozen in air (Fig. 3A): here the cells were found to abut an electron-dense amorphous layer superficial to the basement membrane. Similar material containing membranous fragments was observed on the posterior endothelial surface. Intercellular spaces were of normal width with only slight widening of the tight junctions. Lateral cell-to-cell contact was maintained even in the most severely damaged cells. On the other hand corneas frozen in medium, whether 2

Fig. 1 *Light micrographs of cryopreserved corneas fixed immediately after thawing and removal of Me₂SO. Tissue was fixed in formol saline and stained by haematoxylin and eosin. Scale bars are 100 µm.* A: *Normal, unfrozen cornea.* B: *Cornea frozen in air after equilibration in 2 M. Me₂SO-CPTES. The number of endothelial cells has not been reduced but there is partial detachment from Descemet's membrane. The stroma is swollen, and the epithelium is variable in thickness and vacuolated.* C: *Cornea frozen in 5 ml of 2 M. Me₂SO-CPTES. Some of the endothelium has been lost.* D: *Cornea frozen by Capella and colleagues' method. The endothelium is completely detached, though cell-to-cell adhesion is maintained.*

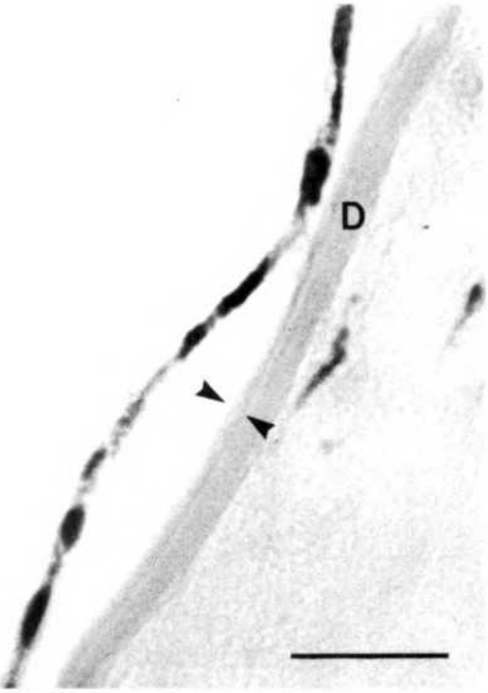

Fig. 2 *Light micrograph demonstrating an amorphous layer attached to Descemet's membrane. The cornea had been preserved by the Capella and colleagues' method, and was stained with haematoxylin and eosin. The scale bar is 20 µm. Note the detached endothelial cells and the amorphous layer (arrowed) on the surface of Descemet's membrane* (D).

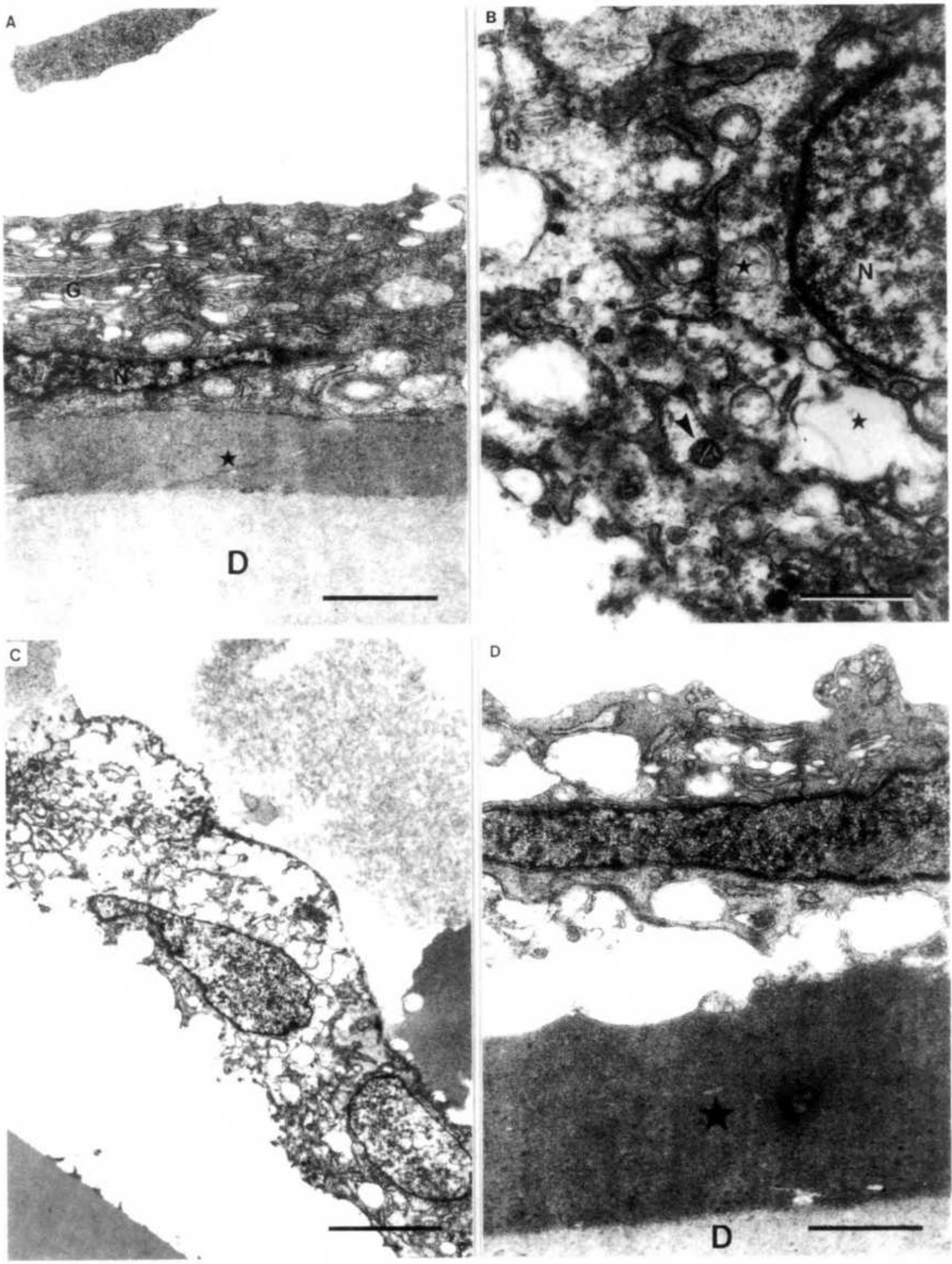

Fig. 3

Table 1 *Results of cornea grafts*

Group	*Postoperative Clarity**	*Post mortem stromal thickness (μm), mean±SEM*
Control n=4	++	322±10
2 M.Me$_2$SO-CPTES frozen in air n=5	++ to +	422±37
2 M.Me$_2$SO-CPTES frozen in medium n=5	+	479±45
Capella and colleagues' technique n=5	+	465±32

*Graft clarity assessed by slit-lamp biomicroscopy.
++=Clear.
+ =Slight opacification, iris details visible.

M.Me$_2$SO-CPTES or Capella and colleagues' solution (Fig. 3B–D), showed extensive detachment of the endothelium from the basement membrane. Most of the cells were severely disrupted, though there were some areas where damage was less severe. The electron dense amorphous layer, varying in thickness from 0·1 to 2·5 μm, was again seen between the endothelium and the basement membrane.

TRANSPLANTATION

Table 1 shows the postoperative appearance and post-mortem stromal thickness of the transplanted corneas. Epithelial damage was observed in all grafts, but surgical problems were rare, including only localised iris synechiae to the wound and peripheral vascularisation in two cases.

Fig. 3 *Electron micrographs of cryopreserved corneas fixed immediately after thawing and removal of Me$_2$SO.*
A: *Cornea frozen in air after equilibration in 2 M.Me$_2$SO-CPTES. Endothelium is separated from Descemet's membrane* (D) *by an amorphous layer* (★). *Some mitochondria appear normal, whereas most show some disorganisation of the cristae, but there is no gross swelling. N=nucleus. G=Golgi apparatus. Bar=1 μm.* B: *Cornea frozen in 5 ml of 2 M.Me$_2$SO-CPTES. Some mitochondria are condensed (arrow) but most are swollen* (★). *The nucleus* (N) *shows slight margination of heterochromatin, and the rough endoplasmic reticulum is vesiculated. Bar=1 μm.*
C: *Lower power view of cornea frozen in 5 ml of 2 M.Me$_2$SO-CPTES. The endothelial cells are severely disrupted, but the intercellular junctions remain intact. The endothelium is detached from Descemet's membrane and is overlaid by amorphous debris. Bar=5 μm.* D: *Cornea frozen by the Capella and colleagues' method. A thick amorphous layer* (★) *is seen between the Descemet's membrane* (D) *and the disrupted endothelium. Mitochondria are swollen. Bar=1 μm.*

Non-frozen controls

All the control corneas were clear, and the range of post-mortem thickness (322±10 μm, mean±SEM, n=4) was similar to that of normal corneas in adult Dutch rabbits (321±8 μm, n=14). In-vivo specular microscopy revealed normal endothelium with only small areas of damage estimated at less than 5%. Histological examination showed an intact endothelium that was firmly adherent to Descemet's membrane (Fig. 4A) and discontinuous from the host endothelium. There was minimal inflammation in the stroma. The epithelium was thin and ulcerated.

Cryopreserved corneas

General appearance. Immediately after being thawed the cryopreserved corneas appeared thin and clear, but they swelled rapidly. More pressure than normal was required to trephine the disc, and desquamation of both epithelial and endothelial surfaces occurred despite careful surgical technique. The discrepancy between host and graft corneal thickness made it difficult to achieve perfect wound closure.

Postoperative clarity. Three of the corneas frozen in air remained clear; two showed a slight haze, which was more marked in the epithelial than the endothelial layer. Corneas frozen in medium, whether 2 M.Me$_2$SO-CPTES or Capella and colleagues' solution, were clear initially but all developed a mild opacification of both epithelial and endothelial layers.

Specular microscopy. In-vivo specular microscopy showed a dark background with bright spots and indistinct lines, but endothelial cell outlines could not be identified. There were no apparent differences between the three experimental groups. The brighter illumination available with the in-vitro specular microscope made it possible to identify the outlines of enlarged endothelial cells, with bright nuclei, in those corneas frozen in air but not in either of the other two groups. Measurement of corneal thickness on the in-vitro microscope revealed swelling to approximately 150% of control values in all groups: the lowest mean value was obtained with the corneas frozen in air, but there were no statistical differences between the groups.

Histology. Corneas frozen in air had an intact layer of endothelial cells over Descemet's membrane, though the cells were decreased in number and poorly adherent (Fig. 4B). The stroma was thickened, keratocytes were scanty, and the epithelium was thin and ulcerated. The corneas frozen in medium, whether 2 M.Me$_2$SO-CPTES or Capella and colleagues' solution, had very few residual endothelial cells (Fig. 4C and 4D), and those were vacuolated. In all groups the host and graft endothelium was discontinuous (Fig. 4E). Fibroblasts

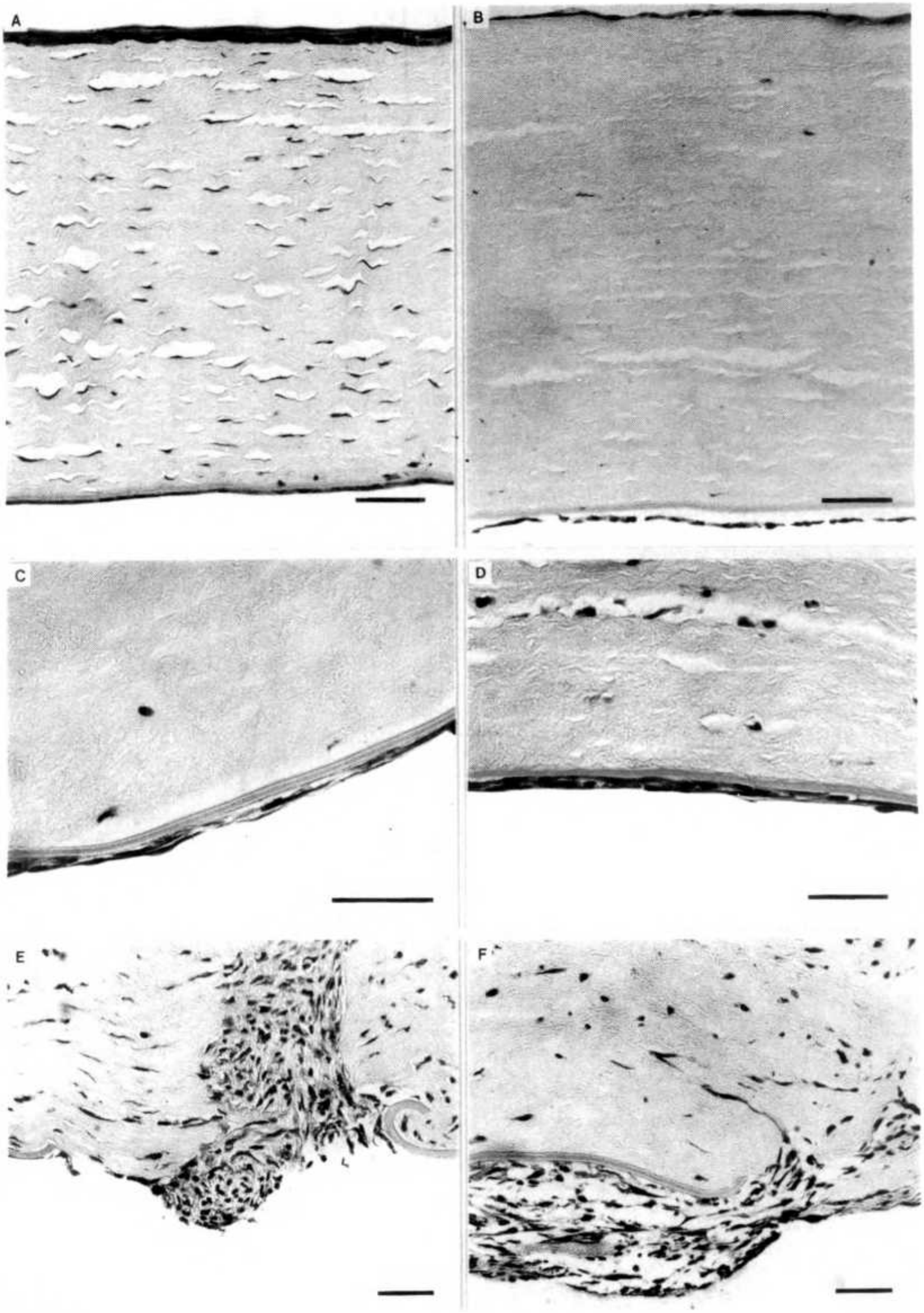

Fig. 4

extending from the wound edges had replaced endothelium over an estimated 20–60% of the graft surface (Fig. 4F). The stroma was thicker than in corneas frozen in air, keratocytes were scanty, and again the epithelium was thin and ulcerated.

Discussion

Effective methods for the long-term preservation of the cornea would facilitate transport of graft material, allow more efficient elective surgery, eliminate wastage, and could make tissue-typed corneas readily available for appropriate high-risk patients. Cryopreservation offers such a prospect, but neither the method of Mueller and colleagues[1,3] nor that of Capella and colleagues[2,4] has proved satisfactory in clinical use. In this study two newer methods have been compared with Capella and colleagues' technique: assessment was by structural studies carried out immediately after removal of the cryoprotectant following thawing, and by corneal transplantation. Transplantation is clearly the most important criterion: it has been used in previous animal experiments[17,18] and in clinical practice.[3,4] Although grafting subjects the cornea to the stress of surgical manipulation, it also offers an ideal physiological environment for such recovery and repair as might be possible, and it is most relevant to eventual clinical application.

In the present study we used the rabbit, and the problems associated with this choice should be noted. We observed epithelial damage in all grafts, and this was attributed to an inadequate tear film: the rabbit blinks unilaterally and slowly, and is prone to incomplete closure of the lids. Consequently evaporation from the rabbit cornea can control corneal thickness even in the absence of endothelial activity, and this must be taken into account in assessing the results.[19] In addition, mitotic activity occurs in the rabbit endothelium,[20] but to avoid this problem we used rabbits older than 6 months and killed the animals after one week. Provided proper attention is given to these problems, the rabbit is a satisfactory experimental animal for the present purpose.[21]

Effective cryopreservation requires the use of protective additives to overcome freezing injury, yet the precise mechanisms involved are still a matter of debate. It has been established that intracellular ice is generally lethal,[22] but most practical cooling conditions produce only extracellular ice. It is unlikely that intracellular freezing occurred in our experiments, though we cannot prove that it did not. It has been thought that extracellular ice is innocuous, and that the essential mechanism of freezing injury is a consequence of the increase in solute concentration that follows the separation of water to form ice.[23] However, it is becoming increasingly clear that extracellular ice may indeed be an important damaging factor not only in cell suspensions,[24] particularly when the cells are present at a high density,[25] but especially in tissues[26,27] and whole organs.[28] Cryoprotectants act by reducing the amount of ice that is formed at any given subzero temperature.[29] This has the effect of mitigating the rise in salt concentration and increasing the unfrozen portion of the system. Control of rates of cooling and warming is important, because this affects the probability of intracellular freezing, recrystallisation processes during warming, and the rate at which damage from high salt concentrations can occur. However, and contrary to popular belief, there is little evidence that it is important to control the temperature at which freezing occurs or the rate at which the latent heat of fusion is removed.[30] Dimethyl sulphoxide is probably the most generally used cryoprotectant at present; in these experiments it was used in each of the three techniques investigated.

Examination of the thawed corneas immediately after removal of the Me_2SO revealed extensive endothelial damage in all groups. However, it was striking that, although the adherence of the endothelial cells to the basement membrane was poor, lateral attachment between the cells remained substantially intact. It is important to note that, when endothelial monolayers are viewed in flat-mounted preparations—for example in histochemical staining methods and scanning electron microscopy—detachment from the Descemet's membrane would not be apparent. Another notable feature was the layer of amorphous material interposed between the basal endothelial surface and Descement's membrane. This layer was present in varying degrees in all the samples examined. It contained membranous fragments and appeared to have been extruded from the damaged endothelial cells, possibly by an exotropic

Fig. 4 *Light micrographs of corneas after grafting. One week after grafting, the corneas were excised and fixed in formol saline and stained with haematoxylin and eosin. Scale bars are 50 µm.* A: *Control corneal graft.* B: *Corneal graft, preserved by freezing in air after equilibration in 2 M.Me_2SO-CPTES. Endothelium appears to be poorly adherent to Descemet's membrane. Stromal keratocytes are reduced in number and the epithelium is thin.* C: *Corneal graft preserved by freezing in 5 ml of 2 M.Me_2SO-CPTES. The stroma is swollen and a fibrous membrane has replaced the endothelium.* D: *Corneal graft preserved by Capella and colleagues' method. Fibroblasts have replaced the endothelial cells.* E: *Control graft showing a wedge of fibrous tissue at the junction of host and graft tissue.* F: *Corneal graft preserved by freezing in 5 ml of 2 M.Me_2SO-CPTES. An extensive growth of fibroblasts has replaced the graft endothelium.*

blebbing process.[31] All the cryopreserved corneas were damaged, and no completely normal endothelial cells were seen in any frozen cornea. However, electron microscopy showed that the endothelium of corneas frozen in air was less severely damaged than in the other two groups.

'Success' of the transplanted cornea may be defined by three criteria: a clear graft, a cornea less than twice its normal thickness, and a complete endothelial cell layer. On this basis only those corneas frozen in air after equilibration with 2 M.Me$_2$SO-CPTES solution can be graded as successful—three complete successes while two, which were slightly cloudy, were regarded as partial successes. None of the corneas that was frozen in medium qualified as successful. In those experiments partial survival of the endothelial cells was associated with decreased clarity and increased corneal thickness. It was not possible to differentiate between either of these two groups by any of the methods used.

It is difficult to compare our results with those previously reported by others, since the method of assessment was quite different. Many such grafted corneas required several weeks to become clear,[17] and when careful cytological analysis was carried out[18 32] the results were less impressive and probably comparable, had the methods of assessment been similar, to those reported here. Histological examination of the grafted corneas at one week showed that those that had been frozen in 2 M.Me$_2$SO-CPTES medium or Capella and colleagues' solution were only partially covered by surviving endothelium, and fibroblasts were found to have repopulated the areas where the graft endothelium had failed to survive. In all cases the graft and host endothelium were discontinuous, and there was no duplication of Descemet's membrane such as would be expected had there been regeneration of endothelial cells,[20] though one week would be early for such duplication. The surviving cells were reduced in number, enlarged, vacuolated, and poorly adherent to the basement membrane. Mueller[1] had previously observed such giant cells, and it has been proposed by Neubauer *et al.*[33] that their formation may be due to the coalescence of several damaged cells. These pathological giant cells were clearly distinguishable from the giant cells that are quite commonly seen in healthy rabbit corneas.[34] The reduced number of cells per unit area of cornea in the present experiments is in agreement with the quantitative results of Clifton and Hanna,[32] Ruusuvaara,[35 36] and Ehlers *et al.*[37] Corneas transplanted after freezing in air had much more complete endothelial layers one week after grafting.

The superiority of corneas frozen in air over those frozen in medium does seem to be clearly established. This observation was first made by Mueller[1] on corneas transplanted in dogs and was later confirmed by Taylor *et al.*[8] who repeated Mueller's cryopreservation method in the rabbit but assessed function by in-vitro specular microscopy. Sperling[38] found that the proportion of cryopreserved bovine corneal endothelial cells that excluded trypan blue depended on the volume of solution in which they were frozen; the optimum volume was about 1·5 ml for an 11 mm button in vials similar to ours. More recently Madden and Easty[39] have confirmed the value of freezing pig and rabbit corneas in air. The present experiments do not indicate why this technique should be better than the others. It has been established that the distribution of ice within smooth muscle tissue is altered by freezing in air rather than medium,[26] and it is known that the pattern of ice formation affects functional recovery in this and other tissues.[27 28] Therefore it seems reasonable to propose that changes in the distribution of ice are responsible for the beneficial effect of freezing in air. It is also possible that ice forming between the endothelial cells and Descemet's membrane is responsible for the separation of these two layers.

Clearly these experiments do not provide convincing support for the clinical transplantation of cryopreserved corneas. They do, however, suggest that corneas are better preserved by freezing in air than while immersed in the preservation solution. Further studies, by more precise techniques to quantify the physiological and cytopathological changes that result from freezing, are now needed to elucidate the mechanisms proposed above and to improve the functional quality of cryopreserved corneas.

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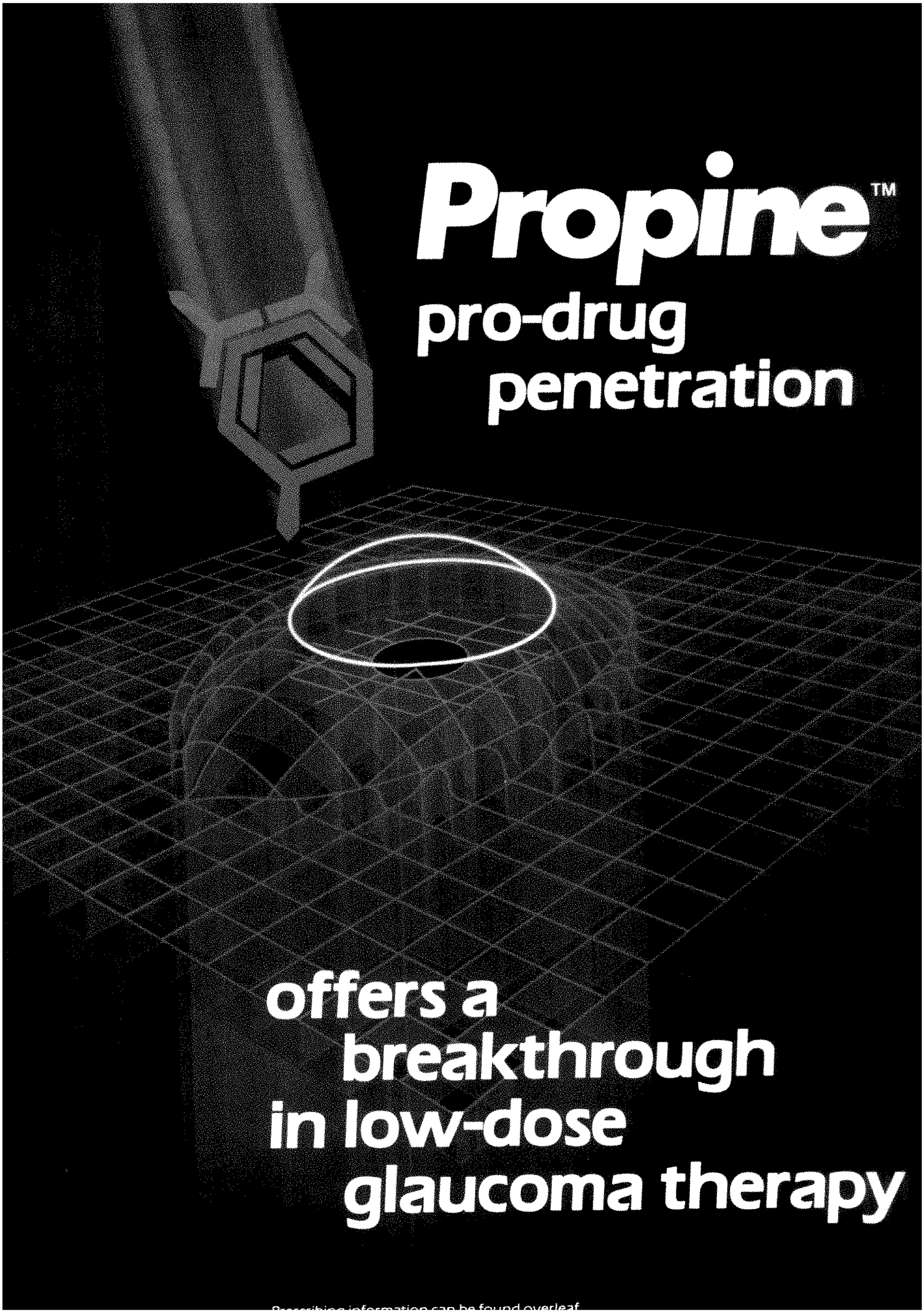
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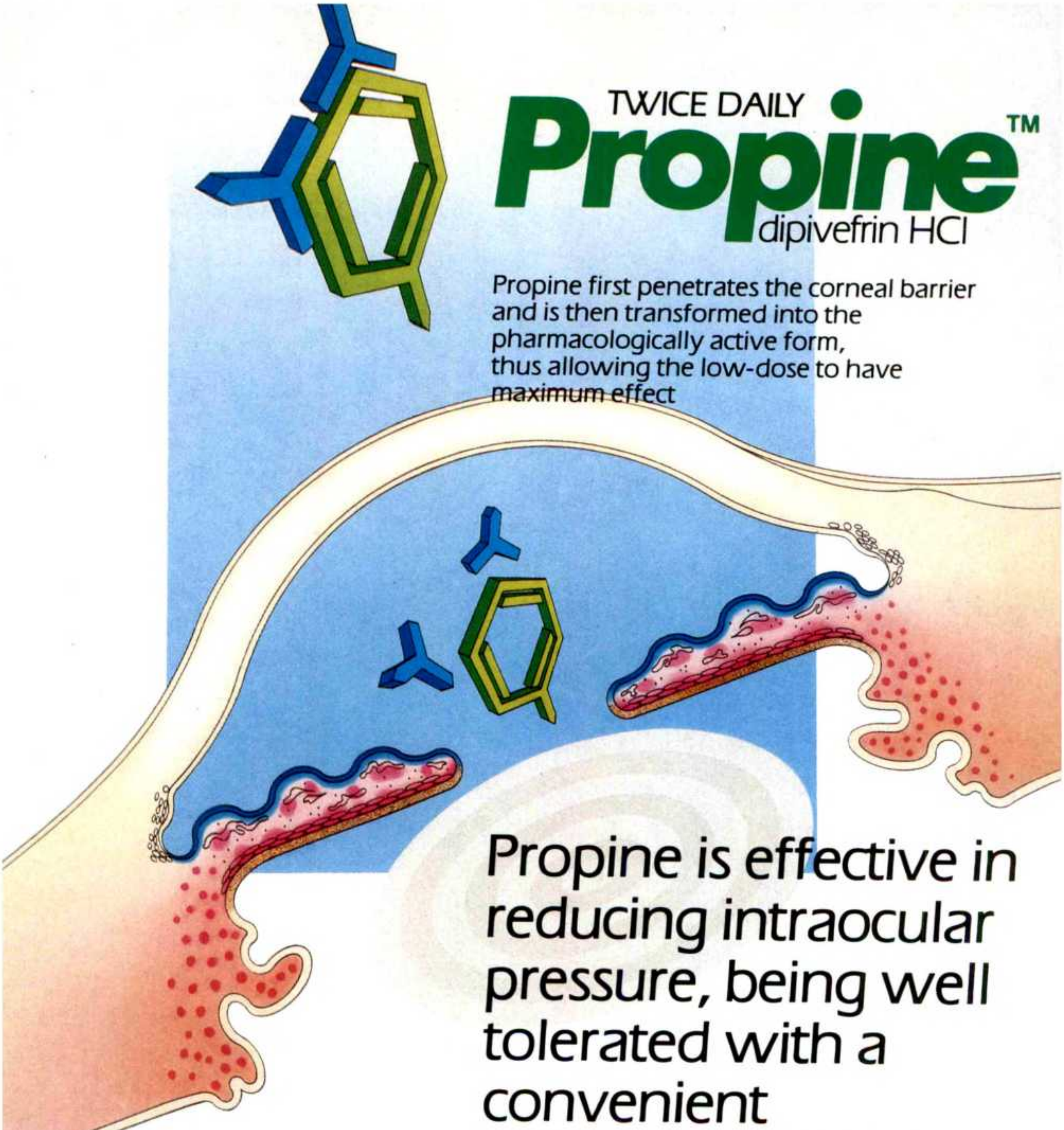

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Double-blind controlled trial to compare anti-inflammatory effects of tolmetin 2%, prednisolone 0·5%, and placebo in post-cataract extraction eyes

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SUMMARY This paper compares the efficacy of tolmetin, prednisolone, and placebo (vehicle only) in controlling post-cataract extraction inflammation in a double-blind trial involving 120 patients. Seventeen patients were excluded from analysis. The results of the 103 patients analysed showed that 94% of the prednisolone treated group was judged to have been successfully treated as compared with 53% of the tolmetin treated group and 46% of the vehicle treated group. The differences between the prednisolone treated group and the other two groups were statistically significant ($p<0·001$). No statistical significance was found between the tolmetin and vehicle groups.

Tolmetin is a non-steroidal anti-inflammatory drug (NSAID) which acts by inhibiting prostaglandin synthesis.[1] Animal studies have shown tolmetin to reduce the level of inflammation in anterior uveitis.[2] These studies have also shown that tolmetin did not tend to raise intraocular pressure as can be the case with prolonged use of topical steroids.[3]

The use of topical steroids following cataract surgery is common practice, and it is not unusual for this treatment to be continued for several weeks, which can lead to a rise in intraocular pressure.[4,5] An agent controlling postoperative inflammation without this effect would be a useful addition to the clinician's armoury. This has led to a double-blind controlled clinical trial to compare the efficacy of tolmetin 2%, prednisolone 0·5%, and placebo (tolmetin vehicle) in the inflammation following uncomplicated intracapsular cataract extraction.

Material and methods

One hundred and twenty patients for intracapsular cataract extraction without intraocular lens implantation were selected for study. Table 1 shows the parameters recorded preoperatively and postoperatively for five days, and then at two and six weeks. More frequent examinations were performed if clinically necessary.

The following criteria excluded patients from the trial: (1) current treatment with systemic anti-inflammatory agents; (2) glaucoma, uveitis, or corneal disease; (3) operative use of α-chymotrypsin; (4) age under 60.

The study was randomised, doule-blind, and conducted at two centres concurrently. Randomisation

Table 1 *Parameters recorded*

Symptoms	
Watering	0=absent
Photophobia	1=mild
Pain	2=moderate
	3=severe
Signs	
Ciliary injection	0=absent
Aqueous cells	1=mild
Aqueous flare	2=moderate
Keratic precipitates	3=severe
Pupil diameter	0=well dilated
	1=moderately dilated
	2=poorly dilated
Intraocular pressure	mmHg

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Table 2 *Reasons for exclusion from analysis*

Reason	*Tolmetin 2%*	*Vehicle*	*Prednisolone 0·5%*
Missing records	1	0	2
Concurrent treatment with anti-inflammatory drugs	3	2	2
Could not applanate	0	0	1
Hypopyon on day 1	2	0	0
Lost to follow-up	0	3	1
Total	6	5	6

Table 3 *Summary of results*

Parameter	*Tolmetin 2%*	*Vehicle*	*Prednisolone 0·5%*
Total patients	34 (100%)	35 (100%)	35 (100%)
Successful treatment	18 (53%)	16 (46%)	32 (94%)
Treatment failures	16 (47%)	19 (54%)	2 (6%)
Episode of IOP >22 mmHg	6 (18%)	3 (9%)	7 (24%)
Discomfort	7 (21%)	4 (11%)	0 (0%)

was achieved by a blocked randomised code, balanced for treatments every 15 patients. Informed consent was obtained from all participants, who were given a trial number which allocated them to one of three groups: (1) tolmetin treated; (2) vehicle treated; (3) prednisolone treated.

Patients were examined by one of three ophthalmologists, who recorded the above parameters using a modification of the method described by Hogan.[6] In order to standardise the scoring system a pretrial assessment of five patients was performed by the three ophthalmologists. The method of cataract extraction was standardised so far as was possible to the use of a limbus-based conjunctival flap, scleral section, one peripheral iridectomy, cryoextraction, and closure with five interrupted 8/0 virgin silk sutures. All patients received treatment with the allocated trial drops and chloramphenicol drops, both four times daily. Mydriatics were used only if indicated.

The trial was concluded at six weeks. Patients who developed an adverse reaction or showed increasing inflammation during the trial period were withdrawn, and suitable alternative treatment was prescribed. Patients who still had inflammation at the end of the trial period were considered treatment failures, and suitable alternative treatment was prescribed. Successful treatment was considered to be resolution of postoperative inflammation within six weeks, with no adverse effects and requiring no additional or alternative treatment.

Results

Of the 120 patients entered into the trial 17 were excluded from analysis for various reasons (Table 2).

Of the 103 patients analysed, 34 received tolmetin, 35 received vehicle, and 34 received prednisolone. The results are summarised in Table 3. Apart from a statistically significantly lower proportion of males to females in the vehicle group, compared with the other two treatment groups, no major imbalance in age, race and side treated between treatment groups was detected (Table 4).

Eighteen out of 34 (53%) of the tolmetin treated group and 16 out of 35 (46%) of the vehicle treated group were considered to have been successfully treated as compared with 32 out of 34 (94%) patients in the prednisolone treated group. The differences between the prednisolone group and the other groups were highly significant ($p<0·001$, χ^2 test), but no significant difference between the tolmetin group and the vehicle group was demonstrated.

Sixteen out of 34 (47%) of the tolmetin group, 19 out of 34 (54%) in the vehicle group, and two out of 34 (6%) of the prednisolone treated group were judged to be treatment failures. From the total symptom scores tolmetin (85%) and prednisolone (97%) appeared to relieve the symptoms of inflammation similarly and significantly better than vehicle (63%).

Although six out of 34 (18%) of the tolmetin group, three out of 35 (9%) of the vehicle group, and seven out of 34 (24%) of the prednisolone group had intraocular pressures over 22 mmHg during the trial, these differences were not found to be statistically significant. Seven out of 34 (21%) patients in the tolmetin group and four out of 35 (11%) in the vehicle group reported discomfort, with the drops ranging from smarting and stinging to one case of severe burning sensation. No discomfort was reported in the prednisolone group.

Discussion

The results of this study indicated that prednisolone was the most effective treatment in reducing the clinical signs of inflammation and patient symptoms. It was also the best tolerated treatment.

There was no statistically significant difference between tolmetin and its vehicle in the resolution of postoperative inflammation. This suggested that the inflammation which follows surgical trauma can be self-limiting. However, tolmetin was significantly more effective than its vehicle in relieving symptoms. It could be inferred from this that tolmetin has an anti-inflammatory effect which is limited to the external ocular structures. This would cast doubt on the ocular penetrance of the drug in man, despite

Table 4 *Analysis of treatment groups*

Parameter	*Tolmetin 2%*	*Vehicle*	*Prednisolone 0·5%*
Age			
Mean	76	75	73
Range	63–99	60–92	35–91
SD	8	7	10
Sex			
Male	13 (38%)	6 (17%)	11 (32%)
Female	21 (62%)	29 (83%)	23 (68%)
Side			
Right	17 (50%)	19 (54%)	17 (50%)
Left	17 (50%)	16 (46%)	17 (50%)

animal studies which have shown that both 2% and 5% tolmetin gain access to the anterior chamber (D Gilbert, personal communication). The potential advantage of tolmetin in being less likely to raise intraocular pressure was not confirmed in this study.

A previous study showed no statistically significant difference between tolmetin, prednisolone, and placebo in reducing inflammation in acute endogenous, non-granulomatous anterior uveitis.[7] These studies on the use of topical non-steroidal anti-inflammatory drugs cast a doubt on their efficacy in the treatment of intraocular inflammation in general. There is no doubt that, when used systemically, NSAIDs have anti-inflammatory activity, as shown by carrageenin induced inflammation.[8]

On the basis of this trial the use of topical tolmetin as a replacement for topical steroids in the treatment of intraocular inflammation cannot be recommended without further research.

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Inferences from beading of a retinal vein draining a choroidal melanoma

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SUMMARY Beading of a retinal vein draining a choroidal melanoma is reported, showing that the endothelial proliferation producing the beading is a response to some blood borne factor(s) traversing the vein and that retinal capillary non-perfusion adjacent to the beaded vein is not a necessary part of the process.

Venous beading is a well recognised sign of proliferative retinopathy in diabetes.[1] It is usually associated with capillary non-perfusion of the adjacent retina. Endothelial cellular proliferation has been demonstrated histologically in the beaded veins.[2] It is uncertain if this proliferation is a response to ischaemia of the adjacent retina or to a factor in the blood passing through the vein from some more peripheral area of ischaemic retina.[3-5]

This paper describes a patient with a prominent beading of a retinal vein draining a choroidal melanoma. The unusual aspect of this case is the absence of any retinal capillary non-perfusion. This indicates that the factor(s) responsible for the beading in this case were carried to the venous endothelium by the blood traversing that vein from the melanoma. Ischaemia of the adjacent retina was not necessary.

Case report

A 57-year-old male was noted to have a 10×12×7 mm moderately pigmented choroidal melanoma in the inferonasal quadrant of his right eye. Vision was 20/25 and the anterior segment was normal. The tumour had a collar button configuration. The inferonasal retinal vein coursed over the tumour and abruptly entered the collar button. This retinal vein showed prominent beading (Fig. 1). Fluorescein angiography showed that this vein filled from the tumour as well as from the surrounding retinal capillaries. It filled at essentially the same time as the other retinal veins, and there was no apparent retinal capillary non-perfusion. It is of note that the angiogram also showed early irregular leakage from an area that appeared most consistent with a small frond of neovascularisation on the distal portion of the collar button (Figs. 2, 3B). This appears to be a second indicator of the angiogenic potency of this tumour.

Discussion

Our patient showed marked venous beading. The unusual aspect of this case is that the affected vein

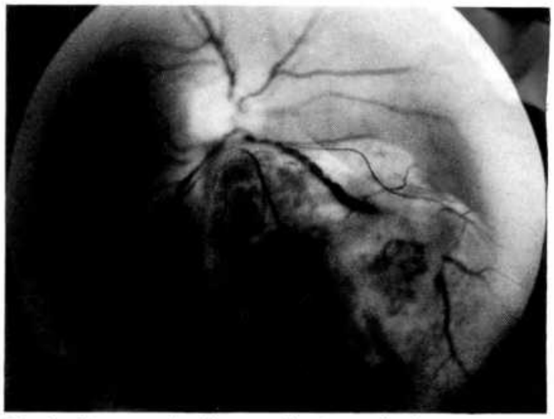

Fig. 1 *Pigmented melanoma showing collar button configuration. The retinal vein overlying the tumour appears to enter the tumour and shows prominent beading.*

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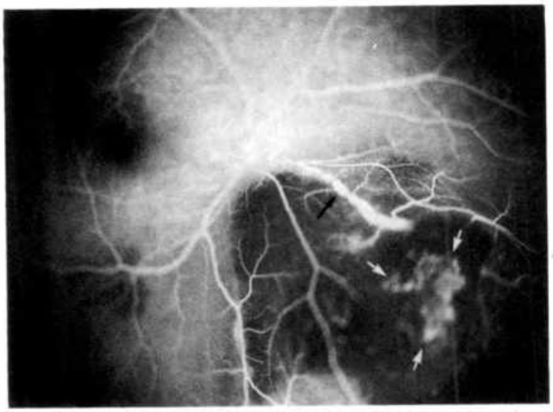

Fig. 2 *Arteriovenous phase angiogram showing normal filling of the beaded retinal vein (black arrow). The surrounding retina shows good capillary perfusion. Some early fluorescein leakage from the area of probable neovascularisation over the collar button is present (white arrows).*

traversed normally perfused retina. This suggests that venous beading is not contingent on surrounding retinal hypoxia. Rather, it appears that some vasoproliferative factor(s) produced by the melanoma influenced tissues downstream and produced the beading in the draining retinal vein. Further evidence of some presumed vasoproliferative factor(s) emanating from the tumour was seen in the tuft of apparent neovascularisation on the surface of the tumour.

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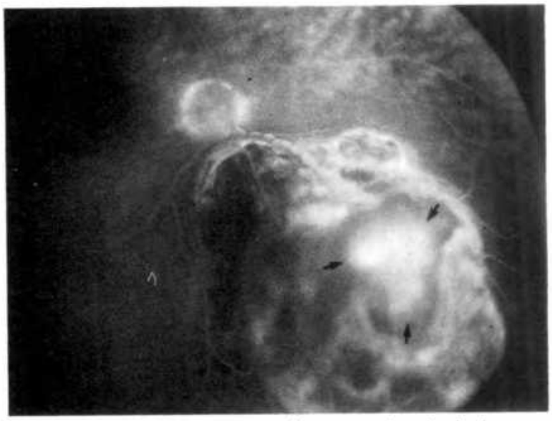

Fig. 3 *Late phase angiogram demonstrating dye leakage from the apparent area of neovascularisation over the collar button (arrows).*

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Photographic recording of slit-lamp appearances of the ocular fundus

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SUMMARY The four methods of illumination in the use of slit-lamp biomicroscopy of the anterior segment, described first by Vogt, are equally useful in the posterior part of the eye. Examination of the ocular fundus is more difficult. In particular, photography of the central and peripheral parts of the fundus demands additional technical arrangements if all the appearances of biomicroscopy are to be recorded.

A major task of medical photography is to record as clearly as possible all the optical details revealed at various examinations.

Each method of examination has to have a counterpart in photography, and each technique of observation must have its equivalent in photographic recording. Hence photographs produced by modern normal and wide angle fundus cameras show the appearances of direct and indirect ophthalmoscopy in a satisfactory way.

For biomicroscopy of the fundus by means of contact lenses an adequate photographic recording is also desirable. The technique of biomicroscopy, particularly of the fundus, demands considerable skill on the part of the examiner and special expertise in the handling of the apparatus. The picture of the morphology of the fundus is built up in the examiner's mind by numerous impressions perceived one after the other by means of different adjustments of microscope and slit-lamp.

Illumination

A. Vogt[1] reported in 1930 on four methods of illumination for the examination of the anterior segment, which can likewise be used for the fundus as follows: focal illumination (broad beam and optical section by narrow beam); retroillumination; specular reflection; and indirect lateral illumination.

Having achieved a clear image by means of different methods of illumination and optical adjustments, the examiner has to select a few settings for the photographic recording which are as typical as possible. This is usually a task for the expert opthalmologist, because a photographer seldom has the knowledge and skill necessary for the taking of such photographs. But the most important prerequisite is to use appropriate technical equipment. This is necessary so that all methods of illumination used in the examination can also be used for the photography.

There is no problem at all in taking pictures with *focal illumination* of the broad beam, but photography of the narrow optical section is less satisfactory, because in this case it is impossible to relate the slit image to a definite area of the fundus. By biomicroscopy the examiner can locate the image of the optical section by changing from a broad to a narrow beam. For photographic recording it is preferable to take photographs of the thin optical section within an illuminated surrounding area. *Retroillumination* is especially suited for the demonstration of structures of the vitreous body or tissue parts that are detached from their plane. Curvature and regularity of shining planes are best evaluated by recording *specular reflections* at zones of discontinuity. Furthermore, this helps to render the narrow optical section more distinctly. *Indirect lateral illumination* is important for the identification of cysts and facilitates the differentiation of solid and semitransparent changes.

Slit-lamp photography of the ocular fundus is based on the same technical equipment as that used in the corresponding photorecording of the anterior segment—that is, a microscope with a beam splitter for simultaneous observation and photography on

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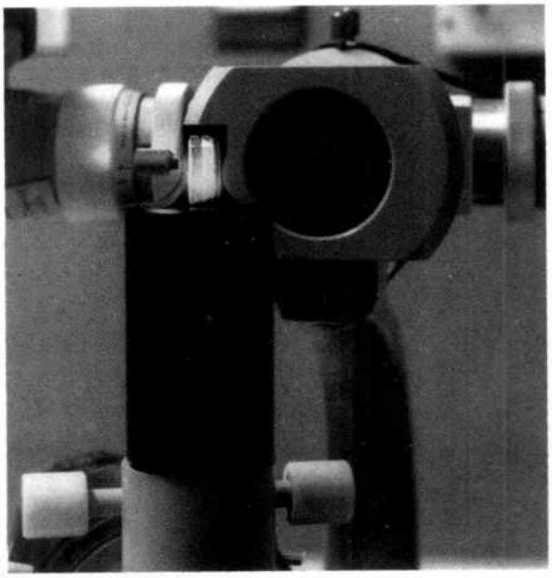

Fig. 1 *Illumination splitter.*

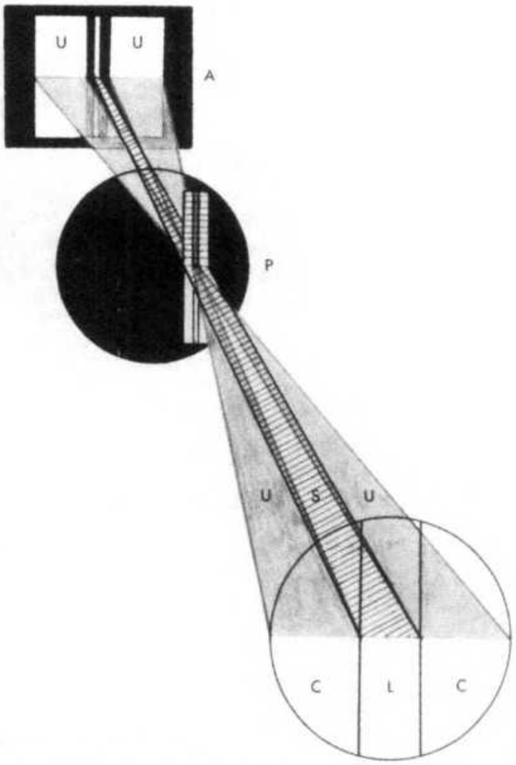

Fig. 2 *Paths of rays of slit and surrounding illumination from the illuminating lens* L *to the plane of the light slit* A. *If the slit light is focused on the retina by a contact lens,* P *corresponds with the point at which the rays pass through the pupil.* U *represents the surrounding illumination.* C *stands for two halves of a cylindrical lens.*

the one hand and a slit illumination of special luminar density, usually provided by an electronic flashlight, on the other.

The equipment required for additional illumination of the surrounding area, as commonly used for the photography of the anterior segment, is unsuitable for the ocular fundus, because the light cannot get there. In this case an illumination-splitter (Fig. 1), introduced by us[2] and produced by Zeiss as a prototype, enables us to project both the slit light and the surrounding illumination (in the shape of two broad slit images) on to the fundus. In the photographic slit-lamp the collecting system focuses both the light of the lamp's filament and also that of the electronic flash tube into the illuminating lens. This in turn refracts the light into the eye under examination. Of the light present in the plane of the illuminating lens only a small part is used for the slit image; the greater part is held back by a slit-shaped shutter in order to render the necessary focal depth to the optical section. Part of this cut off light can be used for the surrounding illumination.

In the case of our illumination splitter the light producing the slit passes through the middle part of the illuminating lens as usual. In front of the rest of the illuminating lens the two halves of a +2·5 dioptre cylindrical lens are placed (Fig. 2). So in the case of fundus examination, two further images of the light slit are generated in front of the slit image. These overlap with the main slit image approximately in the pupillary plane. The bundle of rays then diverge and finally produce two rectangular light fields in the plane of the main slit image—that is, the plane of the occular fundus. These two light fields light up the environment of the narrow optical section and permit its orientation. The broad slit images at both sides of the precisely focused narrow slit image are not exactly focused. A small interval between the narrow optical section and the surrounding illumination allows better recognition of delicate details in the area of the optical section (Fig. 3).

Stereoscopic view

With the sophisticated methods of ocular fundus biomicroscopy the stereoscopic view substantially improved the precise optical resolution of the observed structures. Consequently, for photographic recording, the use of stereophotography is also of crucial importance. It is done without any difficulties by insertion of light splitters connected with cameras in both barrels of the microscope. At the same time

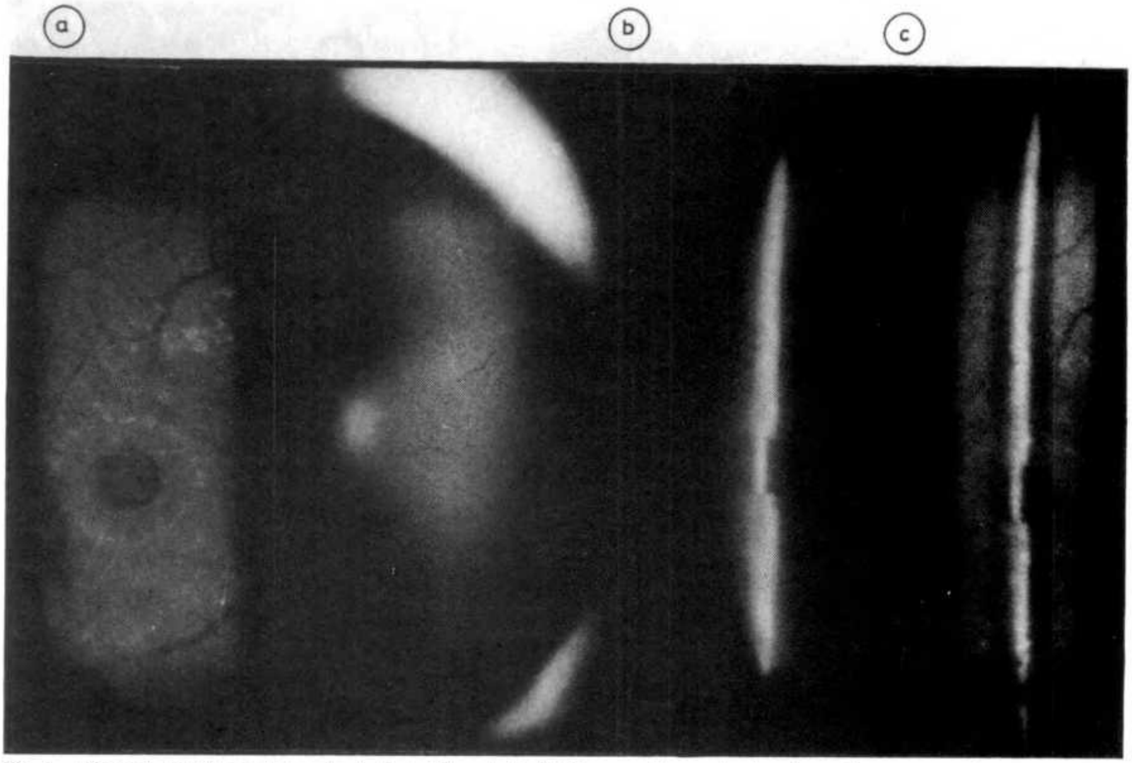

Fig. 3 *Through-and-through macular hole.* (a) *Broad slit.* (b) *Narrow slit—optical section without surrounding illumination.* (c) *Narrow slit—optical section, with surrounding illumination (provided by illumination splitter).*

this complicates the focusing, because now the illumination path of the rays as well as two observation bundles of rays have to be located side by side within the pupil.[3] In this case the ability to overlap the paths of rays of slit and surrounding illumination in the pupillary zone is an exceptional help. The biomicroscopy of the peripheral fundus is done via the Goldmann three-mirror contact lens. The examination of the extreme periphery of the fundus in addition requires the indentation of the bulbar wall. Both techniques can likewise be performed photographically. In the case of stereophotography the picturing of the temporal and nasal fundus periphery is particularly complicated, because the pupillary image is deformed to a longitudinal oval. It is often impossible therefore to position the paths of both illumination and observation rays within the short diameter of the oval pupillary image.

The use of a slit-lamp for patients examined in the supine position,[5] however, enables the satisfactory binocular biomicroscopical examination of the whole lateral fundus periphery. For the photography of these cases a specially adapted operation microscope can be used.

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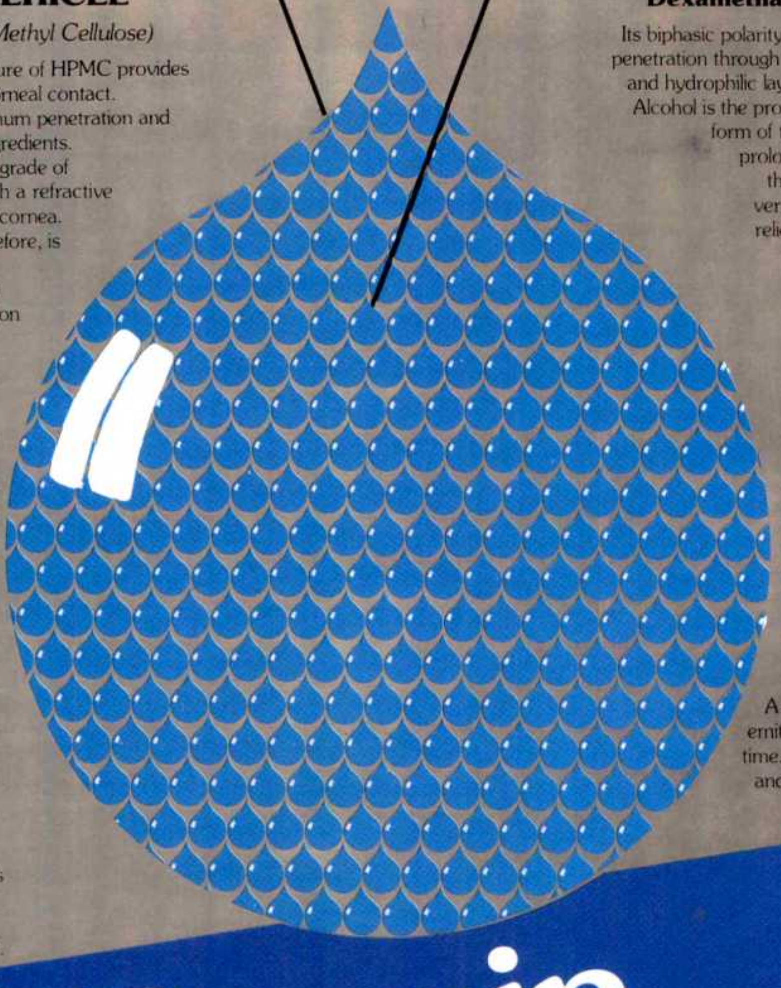

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Sunglasses—an ocular hazard?

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SUMMARY A suggestion that protective eye gear can pose a threat either to the crystalline lens or to the retina is examined from an epidemiological point of view. It is concluded that it may accentuate a pre-existing high-risk hazard but has little significance for low-risk hazards

The so-called 'blue' hazard[1] has raised the question whether the protection of, say, the retina from potentially harmful radiations in one part of the electromagnetic spectrum may increase hazards to the eye due to those coming from another.[2 3] To be specific, if sunglasses reduce the retinal illumination in the visible part of the spectrum and thereby eliminate glare, but are less absorbent in the ultraviolet, what constraints are there for their ultraviolet absorption coefficient in terms of a possible pupillary dilatation resulting from the operation of the light reflex? Anderson and Gebel[2] occupied themselves with this problem but did not directly relate it to ocular hazards. In particular, all these authors failed to take into account the role of the shape of the crystalline lens. The following is an analysis somewhat more elementary than Anderson and Gebel's, but, as the quantitative conclusions which they reached are perfectly consistent with those obtained below, the epidemiological approach followed here may not be without interest.

Results

The relation between the pupillary area A and the retinal illumination I is sigmoid (see Alexandridis[4] and many others). It follows that for one range of I, and only one such range, the rate of change of A with I is maximal (Fig. 1). This remains true even if the experimental data are plotted on logarithmic scales.

A sigmoid variation is typical of dose-response variations. When the dose and the response are both low, an increase in dosage fails to produce much increase in the response. At the other extreme, if the dose is so high as to maximise or to saturate the response, an increase in dosage will be unaccompanied by one in the response. But between the extremes the increase in response caused by a given increase in dosage will evidently come to a peak before declining towards the saturated response values. If we are dealing with a toxin, this maximum increase is determined by the peak sensitivity of the tissue exposed to the toxin.

In our case the analogue of the toxin is radiation and that of the response of miosis. It may be noted in parentheses that, although miosis implies a diminution, the analogy is rendered more satisfactory if the extent of the iridal area is compared with the response. The maximal rate of change of pupillary area with irradiation striking the eye represents the 'worst case' situation: if the pupillary area A decreased at this rate over the whole gamut of illumination I, then wearing sunglasses would lead to a significant pupillary dilatation, with potential hazards due to an increased presence of ultraviolet radiation within the eye. Let this maximal 'worst case' rate of pupillary dilatation be designated by G, because it represents the maximum gradient in the relation between A and I. In other words, it is defined by

$$G=\frac{d\log A}{d\log I}\ \ldots\ldots\ldots\ldots\ldots\ldots\ (1)$$

whence (Fig. 1)

$$A=K.I^{-\alpha}\ \ldots\ldots\ldots\ldots\ldots\ldots\ (2)$$

where K is a scaling constant. Since the light reflex operates via the retina, the illumination I is to be weighted by the effective retinal spectral sensitivity S, so that

$$A=K.[I.S]^{-\alpha}\ \ldots\ldots\ldots\ldots\ldots\ldots\ (3)$$

However, I is variable owing to the absorbance of the sunglasses, if worn; at a wavelength $\lambda(1)$ they transmit $T(1)$% of the incident light. Hence

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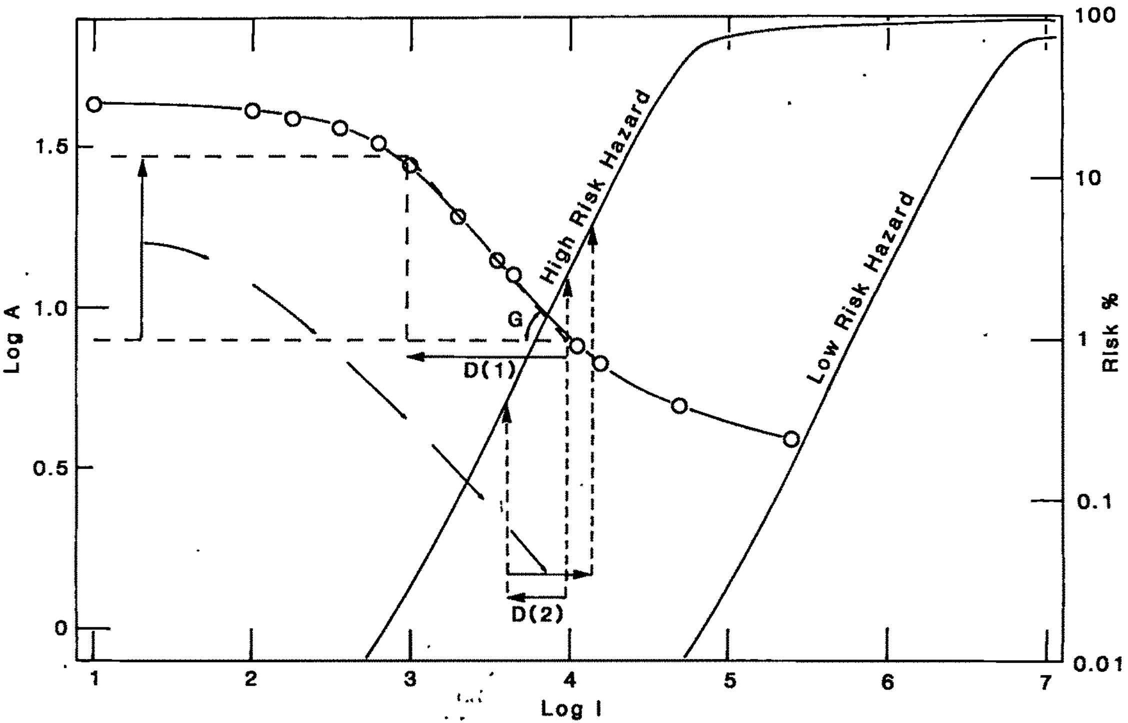

Fig. 1 *Abscissa: log retinal illumination (scot td). Left ordinate: log pupillary area. Right ordinate: risk in percent. Suppose the eye is illuminated with an intensity logI=3·98. At this intensity the risk is 2·5% for a serious hazard but negligible for a low-risk one. When sunglasses with a density D(1)=1 in the visible spectrum are worn, the pupillary area increases maximally by a factor of 3·6 (=antilog of 0·56), as indicated by the arrow on the left. Assume that the density of the glasses for a radiation in the ultraviolet part of the spectrum is D(2). To simplify the presentation, let this also correspond to logI=3·98; the argument does not hinge on this assumption (cf. equation (7)). Consequently the eye will receive from the ultraviolet 3·61 log units, D(2) being chosen as equal to 0·39. However, this reduction is counteracted in this case by the increase in retinal (or lenticular) illumination due to mydriasis, and the risk rises from the original value of 2·5% to 5·4%. If for some reason the pupil had dilated fully after the sunglasses had been put on, it is easy to show that the risk would have climbed to 10·5%. The situation can therefore become grave only if it is serious to begin with: a fourfold rise on the low-risk curve remains what it was originally, namely negligible.*

$$A=K.[I(1).T(1).S(1)]^{-G} \quad \ldots\ldots\ldots\ldots\ldots (4)$$

At another wavelength $\lambda(2)$, the retinal illumination is given by

$$R(2)=I(2).T(2).A \quad \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Let us assume that this radiation represents a potential hazard, and we wish to know whether the worst-case assumption of the dependence of A on I(1), as given by equation (3) can lead to an ocular hazard. Substitution of equation (4) in equation (5) yields.

$$R(2)=K.I(2).T(2).[I(1).T(1).S(1)]^{-G} \quad \ldots\ldots\ldots (6)$$

This relation is more instructive in its logarithmic form:

$$\log R(2)=\log I(2)-G.\log[I(1).S(1)]+\log K-D(2)+G.D(1) \quad (7)$$

where $-\log_{10}T=D$, the photometric density of the sunglasses at any particular wavelength. The first three terms on the RHS of equation (7) are constant. Therefore the retinal illumination at the potentially hazardous wavelength $\lambda(2)$ remains constant if

$$D(2)/D(1)=G \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (8)$$

But D(1) is the density of sunglasses chosen for their perceptible (antiglare) effect; G can equal 0·575.[4] It follows that, on the worst assumption, namely that given by equation (3), the density in a risk, i.e., ultraviolet, region of the spectrum must not be smaller than 60% of that in the yellow-green part of the spectrum, if photic mydriasis due to the wearing of sunglasses is not to increase the risk from ultraviolet radiation. It is in the yellow-green part of the spectrum that the retinal sensitivity S(1) is maximal. Hence glasses, transmitting 5% in the yellow-green part of the spectrum, should not transmit more than 17% for an increased ultraviolet risk to be avoided. If the 'yellow-green' transmission is 10%, then the upper limit is 25%. Since most materials transmit less at short than at long wavelengths unless special tints are introduced, sunglasses become a hazard only under perverse conditions (Fig. 1). Visually useless but allegedly cosmetic blue tints are therefore prime suspects.

Discussion

It may be noted that, from the point of view of a 'blue' or ultraviolet hazard, the approach followed by Anderson and Gebel[2] and above involves a simplification that tends to lead to a measurable under- or overestimate of the actual hazard, depending on whether we are considering the retina or the lens. The reason for this is the shape of the lens, coupled with the fact that it absorbs more light at its centre than near its equator.[5]

Consider first the retina. As the pupil increases, the flux traversing it rises, but less of this will be absorbed by the lenticular periphery than by an equal but central area. Hence the nominal risk to the retina is increased. Now consider the lens. Like all tissues it can be harmed only by radiations which it absorbs. The same increase in pupillary area will add relatively fewer potentially absorbed and harmful quanta than are present in an equal but central pupillary area. Consequently the overall risk to the lens is reduced. It can be shown that this effect can nullify the rise in hazard illustrated in Fig. 1. It would seem to follow, conversely, that the lens may protect the retina at its own expense. It is clinically significant that van der Hoeve[6] was among the first to emphasise that an eye with a cataract is unlikely to present with senile macular degeneration and vice versa.[7] Thus the above analysis should be used with circumspection. Even if, in equation (7), $D(2) < D(1).G$, so that there is a rise in the overall potentially noxious energy entering the eye, the risk, though increased mathematically, may still be negligible.

Suppose that the lens is relatively easily damaged by ultraviolet radiation, but the retina only with difficulty. From our point of view it does not matter whether the relative immunity of the retina is intrinsic or due to some protective filter. Fig. 1 illustrates the risk situation of the two tissues: the curve marked 'High Risk Hazard' refers therefore to the lens, and the other one to the retina. They tell us that much less radiation is needed to damage the lens than the retina. From an epidemiological viewpoint this means that, in a given photic environment, there are likely to be more people with lenticular than with retinal problems attributable to ultraviolet radiation. This is expressed by the risk scale on the right of Fig. 1.

This important aspect helps to put the problem of alleged risks associated with sunglasses into some sort of perspective. The hypothetical mydriasis for the 'worst case' situation indicated in Fig. 1 increases the high risk hazard from approximately 0·4% to 5%, that is from 4 per 1000 persons to 50 per 1000. But, while the fractional increase is analogous on the low risk hazard curve, the number of people affected rises from about 1 per 100 000 to 12 per 100 000, so that we are still dealing with a very small part of the population. These values are merely illustrative. In both types of trauma the real numbers are likely to be appreciably lower. They are determined by the constants in equation (7).

On the face of it this argument seems to be valid for acute exposures. Insufficient information is available to allow a confident assertion that it also holds chronically, when cumulative effects may make themselves felt. But perhaps this analysis helps to point to the minimum number of factors that have to be ascertained if this much more complicated task is to be tackled.

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Retinal cotton-wool spots: an early finding in diabetic retinopathy?

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SUMMARY Five insulin dependent diabetic patients are reported on who had a few small retinal cotton-wool spots or 'soft exudates' either totally isolated or associated with fewer than 10 microaneurysms. These observations suggest that cotton-wool spots may be an early finding in diabetic retinopathy. Significant biological abnormalities in these patients were high levels of glycosylated haemoglobin and mild increases in thrombin generation, indicating slight activation of the coagulation system. The possible significance of these clinical and biological findings is discussed.

A prime aetiological agent in diabetic retinopathy would appear to be chronic hyperglycaemia and the associated metabolic changes of diabetes mellitus.[1] However, the precise causes of both the onset and the development of the characteristic retinal changes seen in diabetic patients are poorly understood. Efforts are increasingly being directed at studying the early stages of diabetic retinopathy in an attempt to find a clue to its pathogenesis.

Microaneurysms and deep punctate haemorrhages appearing first in the posterior retina, particularly temporal to the macula, are usually regarded as the earliest clinical manifestation of diabetic retinopathy.[2,3] This observation has been made in ophthalmoscope and fundus photograph studies of the natural history of the retinopathy found in diabetic patients.[2,3] More recently studies in patients with no clinical evidence of diabetic retinopathy, and by means of refined clinical techniques such as fluorescein angiography[4,5] and vitreous fluorophotometry,[6,7] have shown that leakage of fluorescein from the retinal vessels or the retinal pigment epithelium may precede the development of retinal microaneurysms. However, this finding remains disputed because it has not been confirmed by other investigators.[8-12]

In pathology specimens of diabetic patients retinal capillaries show a definite early loss of intramural pericytes as well as the presence of microaneurysms.[13,14] Microaneurysms and pericyte loss may either be present together or occur in separate areas of the retinal capillary bed. The exact time sequence of these two changes is unknown. As retinopathy worsens in diabetic patients there is an increasing number of totally acellular capillaries which no longer carry blood.[15] It has been suggested that, if complete occlusion of a precapillary arteriole in the superficial layers of the retina occurs suddenly, a cotton-wool spot is seen on clinical examination of the retina.[16-18] However, cotton-wool spots are usually described as part of the advanced preproliferative stage of diabetic retinopathy and where the retinal capillary bed already shows marked abnormalities.[3,17] They may also be seen transiently following improved diabetic control[19-22] In diabetic patients the exact pathogenesis of these cotton-wool spots remains unclear.[23]

We have had the opportunity to examine five insulin dependent diabetic patients in whom small cotton-wool spots, supposedly superficial retinal microinfarcts, were seen in the retina either as the sole diabetic lesion or in association with only a few microaneurysms. Thus, the purpose of this paper is to describe the retinal findings that we observed in these diabetic patients and to discuss their possible significance for the pathogenesis of diabetic retinopathy.

Material and methods

All five insulin dependent diabetic patients were examined at the National Eye Institute (NEI) in Bethesda, Maryland. Ocular examination included best visual acuity, Amsler grid testing, slit-lamp

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examination, and dilated fundus examination, with contact lens examination of the retina. Seven standard photographic fields of the retina, as defined by the Diabetic Retinopathy Study (DRS),[24] were obtained. In three patients (1 to 3) fluorescein angiography of the macula, the area temporal to the macula, and of any field where microaneurysms had been seen on fundus examination was performed in both eyes. Colour vision was assessed by Lanthony desaturated D-15,[25] 100-hue, and chromagraph[26] tests. Contrast sensitivity was also performed in patient 1 by the procedure described by Higgins *et al.*[27]

In all five patients a detailed medical history and a physical examination, including blood pressure and neurological examination, were performed. In all five patients levels of glycosylated haemoglobin were determined by ion-exchange chromatography. In four patients blood was also collected for coagulation studies, without stasis, from an antecubital vein. Routine coagulation screening included a prothrombin time, partial thromboplastin time, thrombin time, and plasma fibrinogen levels.[28] Plasma levels of factor VIII/von Willebrand factor were assessed by a one-stage VIII:C assay, a Laurell assay for VIII-related antigen (VIIIR:Ag), ristocetin cofactor activity assay,[29] and agarose electrophoresis for visualisation of VIIIR:Ag multimers.[30] Plasma levels of fibrinopeptide A (FPA) were measured by a radioimmunoassay (Mallinkrodt, St Louis, MO) and plasma levels of β thromboglobulin (βTG) and platelet factor 4 (PF4) by radioimmunoassays (Amersham, Arlington Heights, IL and Abbott, North Chicago, IL, respectively). Platelet size was determined with a Particle Data Cellozone computerised system.[31] Patients 1 and 2 were seen on a second occasion one year after the first examination, and at that time coagulation studies on them were repeated. We chose not to perform platelet aggregation studies because this in-vitro phenomenon is probably not a quantitatively sensitive method for evaluating platelet activation and is subject to significant technical problems.

In all five patients kidney function was also assessed. Serum blood urea nitrogen (BUN) and creatinine, creatinine clearance, and 24-hour urine collection for 24-hour protein excretion determination were studied. Nerve conduction studies in the right median motor and sensory nerves and peroneal motor nerve were performed in patients 1 and 3.

Case reports

PATIENT 1

This was a 20-year-old white man whose insulin dependent diabetes was diagnosed at 13 years of age.

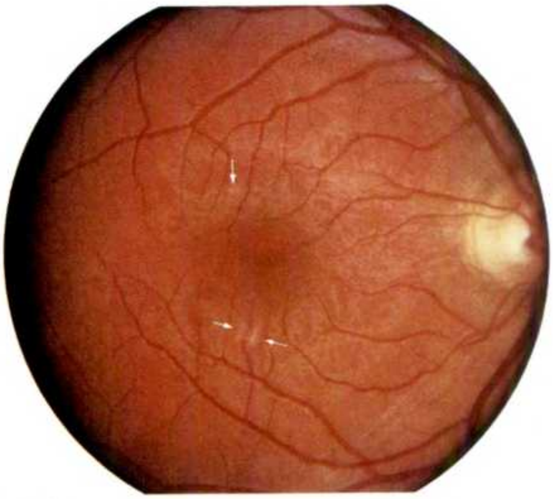

Fig. 1A

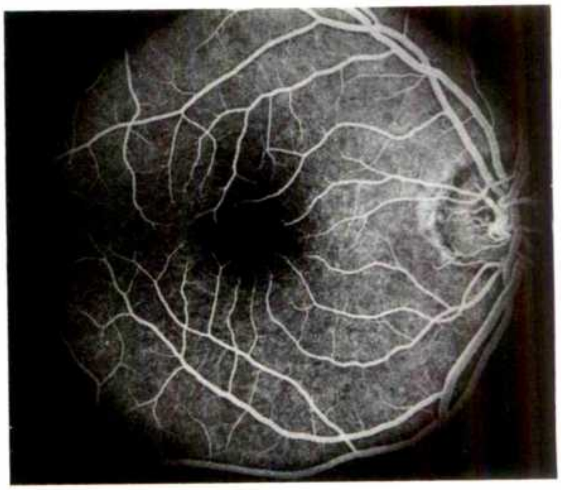

Fig. 1B

Fig. 1 *Patient 1, right eye. A: Three cotton-wool spots in the macular area (arrows). B: fluorescein angiogram showing hypofluorescence in the same locations and two microaneurysms at the posterior pole.*

He received two injections of regular and NPH insulin a day (64 units). He had never had a diabetic coma but had rare episodes of mild hypoglycaemia; he tested his blood for glucose levels once a day. There was no family history of diabetes. Ocular examination was normal except for the right retina, which showed five microaneurysms and four small, elongated superficial grey-white cotton-wool spots in the superior and inferior parts of the macula. These were very prominent on biomicroscopy and fundus photography and corresponded to areas of hypo-

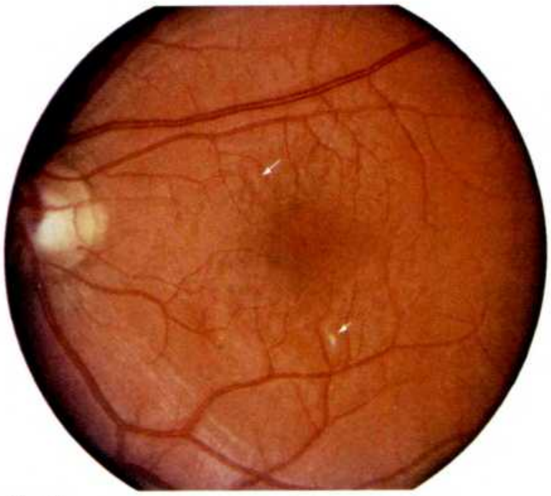

Fig. 2A

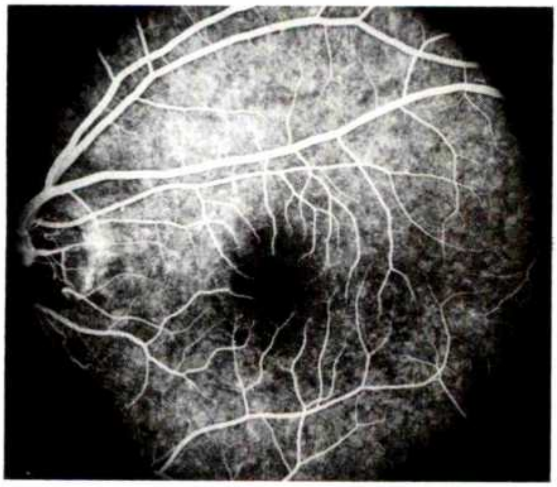

Fig. 2B

Fig. 2 *Patient 1, left eye. A: Two isolated cotton-wool spots in the macular area (arrows). B: Fluorescein angiogram showing hypofluorescence in the same locations and no other diabetic retinal abnormality.*

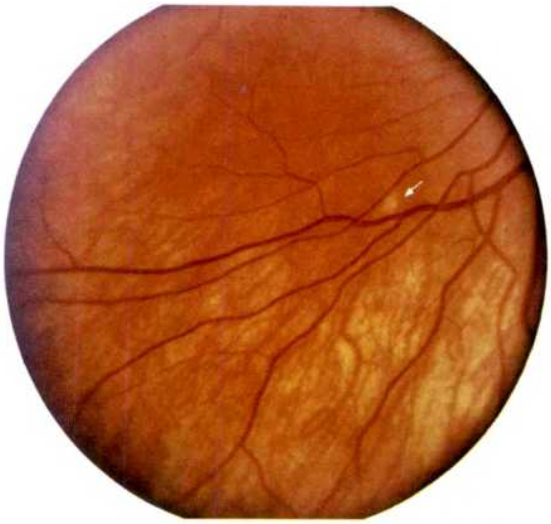

Fig. 3 *Patient 2, left eye. One small cotton-wool spot (arrow) in field 7 of the DRS photographs.*

fluorescence without abnormalities of the surrounding capillary bed on fluorescein angiography (Figs. 1A,1B). In the left eye there were two similar cotton-wool spots in the macular area and no other diabetic lesion (Figs. 2A, 2B).

In each eye central retinal artery diastolic pressure was 39 mmHg. Colour vision tests were normal. Contrast sensitivity studies showed no abnormality in comparison with age matched controls.[27]

The patient had no clinical evidence of diabetic neuropathy but had slower motor nerve conduction velocity (N) in the right median motor (N=49 m/s) and peroneal motor (N=31 m/s) nerves. Standing diastolic blood pressure was 150/88 mmHg. Physical examination was on two occasions normal, as was kidney function. The level of glycosylated haemoglobin was high (13·5%). On two occasions he had a raised plasma fibrinopeptide A (FPA) level and on one occasion a minimal elevation of β thromboglobulin (βTG) and platelet factor 4 (PF4) (Table 1).

At follow-up one and half years later fundus examination revealed in the right eye five microaneurysms and one remaining cotton-wool spot in the macula. In the macula of the left eye there was only one small cotton-wool spot.

PATIENT 2

This was a 33-year-old white man who had had diabetes for four years. There was a family history of diabetes in a great-great-grandmother. He received one injection of 32 units of insulin lente a day. He did not test his urine or blood regularly and had a relatively poor metabolic control, as reflected by the levels of glycosylated haemoglobin (14·4% of normal haemoglobin). Ocular examination was normal except for the left retina, which showed microaneurysms—two at the posterior pole and one along the inferior temporal retinal vein—and in field 7 of the DRS photographs one 100 μm, white, well defined, isolated, rounded cotton-wool spot (Fig. 3). Colour vision was normal.

Physical examination showed nothing abnormal. Blood pressure was normal, 120/72 mmHg in the supine and 132/84 mmHg in the standing position.

Table 1 *Blood coagulation and platelet studies in four insulin dependent diabetic patients with retinal cotton-wool spots*

	FPA ng/ml	*Factor VIII/von Willebrand factor (vW)*				*βTG ng/ml*	*PF4 ng/ml*	*Platelet size* μm^3
		VIII:C	*Ristocetin cofactor*	*VIII R:Ag*	*vW multimers*			
Case 1								
Measurement								
A*	9·6	144%	180%	193%	Normal	53·4	10·1	—
B**	3·4	123%	126%	130%	Normal	33·4	5·1	
Case 2								
A	0·8	77%	103%	135%	Normal	42·6	9·8	6·87
B	2·3	93%	102%	148%	Normal	33·3	5·3	—
Case 3	2·8	75%	91%	90%	Normal	30·5	4·4	7·28
Case 5	3·6	96%	128%	108%	Normal	37·9	4·8	7·28
Normal range†	(0·5–1·3)	(50–150%)	(50–160%)	(58–160%)	‡	(10·6–41.4)	(1·9–10·0)	(4·1–9·0)

FPA=fibrinopeptide A. VIII:C=factor VIII: C activity. VIII R:Ag=factor VIII related antigen. βTG=βthromboglobulin. PF4=platelet factor 4.

†As obtained from a group of 24 normal persons not on medication, age 20–50, with no history of bleeding disorder.

A* results of the first and B** second measurement of these coagulation factors.

‡All multimers visualised and no anomalous bands or abnormally high molecular weight bands seen.

There was no evidence of peripheral diabetic neuropathy. Incomplete bladder emptying suggested some autonomic neuropathy. Kidney function was normal. Coagulation studies showed a slight elevation of fibrinopeptide A (FPA) on one occasion only (Table 1).

One year later the retinal findings were similar except in the left eye, where one flame shaped haemorrhage lay close to the cotton-wool spot which was still present.

PATIENT 3

This was a 25-year-old white woman who was diagnosed as diabetic at 18 years of age. She received one injection of insulin per day, 11 units of regular and 26 units of NPH. She had had one hypoglycaemic coma. She tested her blood for glucose levels twice a day. There was a family history of type II diabetes in a paternal grandmother. Ocular examination was normal except for the retina of the right eye, where there were 10 microaneurysms and one small, grey-white, elongated superficial cotton-wool spot above the macula, and in the left eye where there were six microaneurysms but no other diabetic retinal lesion (Fig. 4). In the right eye colour vision tests showed a mild blue-yellow defect on FM 100 hue and D-15 desaturated tests. Colour vision was normal in the left eye.

Her blood pressure was normal, 104/68 mmHg supine, 98/60 mmHg sitting. The patient had no clinical evidence of diabetic neuropathy, though nerve conduction velocity (N) of the motor peroneal nerve was decreased (N=41 m/s). Kidney function was normal. Glycosylated haemoglobin was raised to 12·7% of normal haemoglobin. Coagulation studies showed slightly increased FPA on the one occasion when it was measured; other coagulation and platelet studies were normal (Table 1).

One year follow-up showed that in the right eye the small cotton-wool spot was still present, and five of the microaneurysms, initially seen close to the fovea, were no longer visible. In the left eye there were nine microaneurysms.

PATIENT 4

This was a 46-year-old white woman who had received insulin therapy for 10 years, one insulin injection of 30 units of lente insulin a day. Examination of visual acuity and anterior segment gave normal results. In the right eye there were three

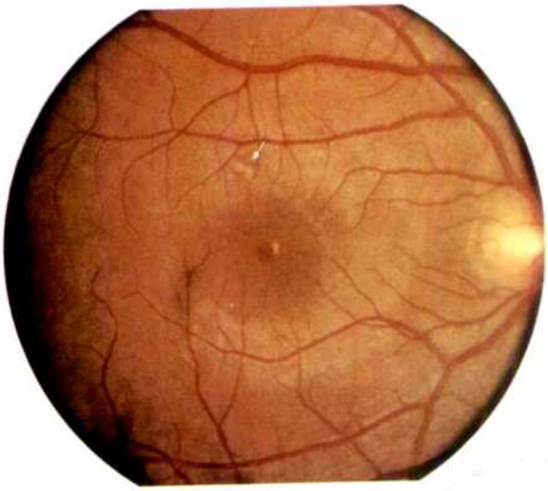

Fig. 4 *Patient 3, right eye. One cotton-wool spot (arrow) above the macula with microaneurysms.*

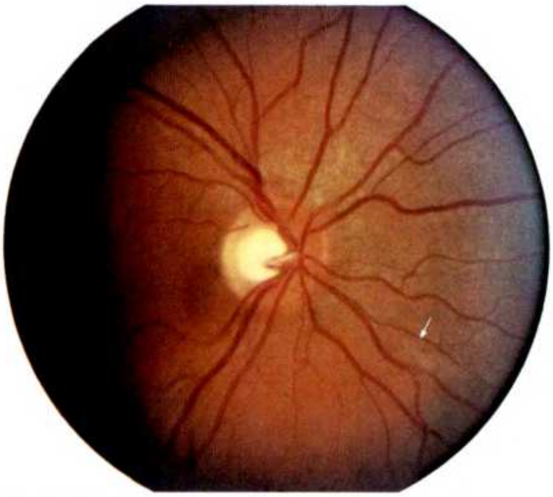

Fig. 5 *Patient 4, right eye. One cotton-wool spot (arrow) along the inferior nasal artery, associated with one microaneurysm.*

microaneurysms at the posterior pole. Almost a disc diameter from the optic disc there was also a small greyish elongated cotton-wool spot along the inferior nasal artery, associated with one microaneurysm (Fig. 5). In the left eye there was only one microaneurysm, inferior to the fovea.

Blood pressure was normal, 124/84 mmHg supine and 118/80 mmHg standing. Physical examination showed nothing abnormal. The patient had decreased triceps and quadriceps reflexes. Serum BUN and creatinine were normal. Glycosylated haemoglobin was 11·3% of normal haemoglobin. Coagulation studies were not available.

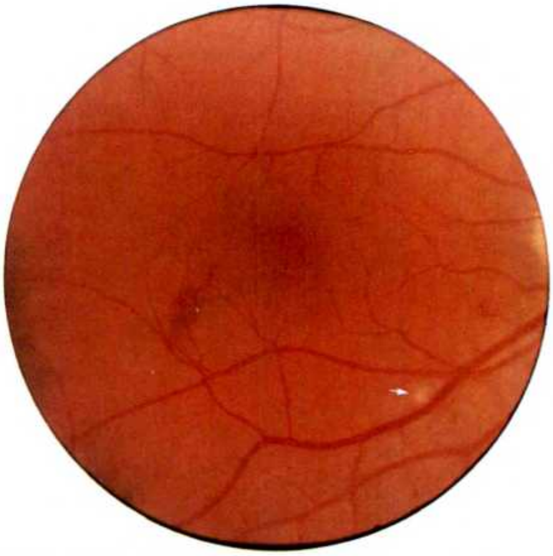

Fig. 6 *Patient 5, right eye. One small cotton-wool spot (arrow) along the inferior temporal vessels. No other diabetic retinal lesion in either eye.*

PATIENT 5

This was a 34-year-old white man whose diabetes was diagnosed at 31 years of age. He received two injections of 10 units of insulin NPH a day and he tested his blood sugar three times a week. There was a family history of type II diabetes in an uncle. Ocular examination was normal except for one small, superficial grey-white, rounded cotton-wool spot along the inferior temporal retinal vessels in the right eye, which had been noted one year before (Fig. 6). Blood pressure was 102/78 mmHg standing and 100/70 mmHg supine. There was no clinical evidence of diabetic neuropathy. Kidney function was normal. Glycosylated haemoglobin was 7·8% of normal haemoglobin. Coagulation studies showed a slight increase in FPA without other abnormalities (Table 1).

Discussion

We report on five young insulin dependent diabetic patients who had small retinal cotton-wool spots or 'soft exudates,' either isolated or associated with only a few microaneurysms elsewhere in the fundus. Independent confirmation of these retinal findings came from the Fundus Photography Reading Center in Madison, where the fundus photographs of patients 1, 2, and 4 had been subsequently reviewed for a separate study.

These cotton-wool spots, though smaller, had a similar appearance to those previously described in diabetic patients,[3 17-19 21 22 31 32] where they were usually seen along the upper and lower arcades of the optic nerve fibres, and also at the border of the disc and out for at least four disc diameters. In two of our diabetic patients, however, the cotton-wool spots were in the macula itself, in the space between adjacent vessels, and this location may have explained their somewhat linear configuration.

Esmann *et al.*[32] have previously noted that cotton-wool spots in the absence of systemic hypertension or renal disease are quite a frequent finding in diabetic retinopathy. In none of our patients was the blood pressure raised either at the initial or at the follow-up examination, and none had any renal abnormality. While in diabetic patients 'soft exudates' may also occur in the mid retinal capillary bed, where they are seen as an area of greying and initially somewhat thickened retina, those occurring in the superficial retinal layers are more easily noticeable. However, these 'soft exudates' may still be easily overlooked by direct ophthalmoscopy, particularly in the macular area of young patients whose retinal reflexes are prominent, and they may be clearly identified only on careful biomicroscopic examination of the retina, as was performed in the present study.

In diabetic patients the appearance of numerous cotton-wool spots is usually indicative of rapidly advancing retinopathy.[3] In our patients, however, there were only a few small cotton-wool spots and no adjacent capillary abnormalities, venous dilatation, retinal haemorrhages, oedema or exudates, or intraretinal microvascular abnormalities (IRMA) to suggest preproliferative diabetic retinopathy.[3] In two eyes the cotton-wool spots were the only diabetic retinal findings. Furthermore in the three patients who were seen at least one year later these soft exudates were still present, while the diabetic retinopathy had not otherwise worsened. In diabetic patients under 40 years of age the mean half life of the cotton-wool spot has been found to be as long as 8·1 months.[17]

Improved metabolic control in diabetic patients with mild to moderate diabetic retinopathy at baseline may also evoke cotton-wool spots and sometimes IRMA, but these lesions appear to be transient and are not followed by the development of proliferative diabetic retinopathy in these patients.[20 22] None of our patients had made any significant change in their insulin regimen during the previous 12 months. Thus cotton-wool spots in different clinical situations may have a different prognostic value and their causes may well differ.

The histological features of the cotton-wool spots that we observed are those of an area of swelling of the nerve fibre layer with cytoid bodies.[16] In diabetic patients the retinal capillaries on trypsin digest preparation of that same area are thin and show hypostaining and loss of nuclei, particularly of mural cells.[16] It has been postulated that cotton-wool spots in diabetes are due to acute focal ischaemia. Ashton[13] has described marked narrowing of the lumen of the precapillary arteriole as a cause of capillary dropout. The reason that narrowing occurs there is not clear. Furthermore this narrowing was described in cases of advanced diabetic retinopathy and might be the result rather than the cause of the collapse of the capillary bed. It remains contentious whether it is microinfarction which is responsible for soft exudates or whether the localised area of capillary closure is a consequence of the local tissue swelling.[23 33]

Whether retinal lesions in diabetic patients are due to a local metabolic disturbance, such as hyperglycaemia with resulting increase in the sorbitol pathway,[34] or to alteration in blood flow secondary to increased blood viscosity,[35-37] or to local hypoxia,[38] is not clear. It is noteworthy that in four of the five patients in the present study the control of their diabetes at the time of examination was relatively poor, as reflected by high levels of glycosylated haemoglobin.

Activation of coagulation factors and platelets has also been implicated in the pathogenesis of vascular lesions in diabetic patients.[39-44] We observed a slight increase of plasma fibrinopeptide A in three of the four patients that we tested. In the coagulation cascade fibrinopeptide A is specifically cleaved from the A α-chain of fibrinogen by thrombin. Therefore our results suggest a rather mild increase in thombin generation in vivo. The lack of increase in the platelet derived proteins (βTG and PF4), as well as normal levels (with one exception) of factor VIII/von Willebrand factor (vWf), indicate no significant platelet activation or endothelial cell release of vWf in the diabetic patients reported on here. No absolute causal relationship between the observed thrombin formation in vivo and the cotton-wool spots can be defined. It does appear, however, that activation of platelets is very unlikely to have played any significant part at this stage in the retinopathy of our diabetic patients.

In summary, we found that five insulin dependent diabetic patients had small retinal cotton-wool spots, either totally isolated or associated with less than 10 microaneurysms, while having no other diabetic retinal lesion. From our observation one might speculate that cotton-wool spots may be regarded as an early change of diabetic retinopathy. Poor metabolic control of the diabetes and mild increases in thrombin generation, suggesting activation of the blood coagulation factors, were the only significant biological abnormalities associated with the retinal lesions in these patients. These findings deserve further investigation for their possible significance in the pathogenesis of diabetic retinopathy.

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The presumed neurotoxic effects of *Catha edulis* – an exotic plant now available in the United Kingdom

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SUMMARY Bilateral optic atrophy is reported in two patients who, although they were long-standing users of the leaves of *Catha edulis*, had chewed larger quantities than usual. Since the leaves of this plant are used widely throughout its native area as the source of a mildly stimulant narcotic, the effect in these cases may be an idiosyncratic reaction to an unusually large dose.

Case 1

A 32-year-old Somali male had worked as a medical assistant in Somalia. After returning from a medical expedition in a remote area of the country he described a period of abnormally large ingestion of a local leaf known as khat, though he had chewed smaller quantities since childhood.

The patient had spent three days relaxing with two friends and chewing khat. The quantity used was considerably more than was usual either for the patient or generally. He obtained little sleep during these three days but after this slept almost contiuously for 36 hours. Before sleeping he had noticed a slight blurring of vision, but he attributed this to fatigue. On waking, the visual disturbance had increased, and the description of symptoms suggested bilateral scotomas. These symptoms increased over the next three days and had apparently remained static since then. Both eyes were affected equally.

The patient suffered no pain and was certain that he had not been subjected to any trauma. There was no history of exposure to any neural toxin other than tobacco and alcohol. Alcohol intake was minimal, amounting to an occasional drink of commercial gin, and he had had none for at least seven days before the visual symptoms appeared. He was a moderate smoker of good quality commercial cigarettes. Diet had remained normal throughout the period. One of the other participants in the khat session had also suffered some visual defect, but he remained in Somalia when the patient came to Britain and has since perished in an air raid.

The patient was a tall, well-nourished negro male. Right visual acuity was hand movements and left was counting fingers, both eccentrically at half a metre. He was virtually emmetropic, and refraction did not improve his vision. Anterior segment examination of each eye was normal, and intraocular pressures were 14 mmHg in each eye. There was no demonstrable afferent pupil defect, and although pupillary light reflexes were sluggish on each side they were symmetrical.

Gross bilateral optic atrophy was present, with pigmentary anomalies at each disc, but no elevation. Blood vessels and retina appeared normal, save for an obvious paucity of retinal nerve fibres in the papillomacular bundle on each side on red-free ophthalmoscopic examination.

Vision field examination was difficult, but with large targets bilateral central scotomas, breaking out into the periphery, were demonstrated. The patient's mobility and behaviour were consistent with this form of visual field defect. Routine haematology scan, VDRL and the fluorescent treponema antibody absorption tests were normal, save for a band of HbA on electrophoresis. Fluorescein angiography was normal apart from gross lack of perfusion in the small vessels of both optic discs. There was a reduction of the electroretinogram (ERG) on flash stimulation. Skull radiography was normal. Since the patient suddenly decided to return to Somalia, a visual evoked response and further neurological examination were not performed. There is no prospect of follow-up.

Case 2

This patient was a 27-year-old Arab who had lived

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most of his life in a small Yemeni community in South Wales. He attended casualty accompanied by his brother, complaining of decreased vision in each eye. He first noticed blurring of vision three months earlier, and it had become worse over a period of approximately one week. Since then his vision had remained static.

His visual acuities were 6/36 left and 6/60 right eye, and he had no significant refractive error. Anterior segment examination was normal and intraocular pressures were 11 mmHg in each eye. Pupillary light reflexes were grossly normal, if rather sluggish. Retinal vessels were normal, but there was a reduction in nerve fibres of the papillomacular bundle in each eye on red-free ophthalmoscopic examination. Both discs were atrophic. Visual fields showed central scotomas. Routine blood scan and skull *x*-rays were normal.

The patient neither smoked or drank alcohol and he had had no serious illness. He took no drugs, but he and his brother admitted chewing imported khat leaves since childhood within the family group. On inquiry the patient said that during the week preceding the onset of visual symptoms he had been staying with friends. These friends had a large quantity of fresh khat leaves, and during this week he had used a much larger quantity than ever before.

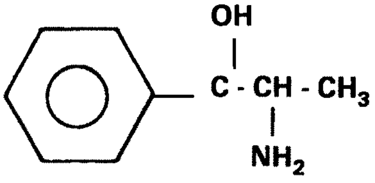
An outpatient appointment was made for further investigations, but unfortunately he failed to attend and efforts to trace him were unsuccessful.

Discussion

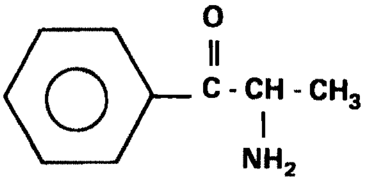
Catha edulis Forsk., or khat, is a member of the family Gelastraceae and has been grown for centuries in parts of eastern Africa and southern Arabia. The fleshy, pinnate leaves are chewed by millions of inhabitants of these countries for the drug's ability to produce euphoria, combat fatigue, and as part of social gatherings.[1] Khat grows at 3000 to 6000 feet (900–1800 m) above sea level and reaches a height of 20 feet (6 m). It is a thirsty plant but can survive drought, and the leaves can be harvested throughout the year. The plant is seedless, and this may explain its limited distribution.[2]

Extensive thin-layer and gas-liquid chromatographic analyses of the fresh leaves of the khat plant have isolated three major compounds: cathine ((+) norpseudoephedrine or phenylpropanololamine), cathinone ((−) alpha-aminopropiophenone), and (−) norephedrine.[3,4] Fig. 1 shows the similarity in chemical structure between cathine, cathinone, and amphetamine.[5] In addition there are vitamins, minerals, and considerable quantities of tannins. Cathine was identified in 1930, and for a long time it was considered to be the only active stimulant in khat.[6] Cathinone was isolated in 1975. It is a ketone congener of cathine, and it is now believed that it is the main active principle responsible for khat's stimulant properties.

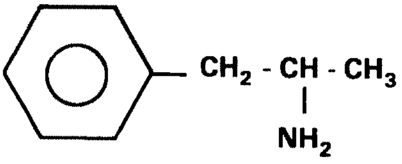
Khat induces amphetamine-like sympathomimetic and central stimulant effects in users. The pharmacological effects include mydriasis, pseudoexophthalmos, tachycardia, extra systoles, hypertension, conjuctival congestion, headaches, and increased respiration. Anorexia and insomnia are also common in habitual users. It has been reported that the central artery pressure is increased up to three times the usual value after khat use.[7] Chewing khat leaves has been shown to cause a reduction of intraocular pressure in both normal and glaucomatous patients in two or three hours.[8,9]



cathine [(+) - norpseudoephedrine]



cathinone [(-) - α - aminopropiophenone]



amphetamine

Fig. 1 *Structural formulae.*

Schizophrenic behaviour has been observed during and after khat use, like the schizophrenia and paranoia following chronic amphetamine absorption.[1] A mania-like psychosis was reported in an Arab student in the USA after he had been seen to chew 24 leaves of a houseplant. The plant was later identified as khat.[5] A similar case of khat-induced schizophreniform psychosis has been reported in a member of a Yemeni community in Liverpool, and there are small Yemeni groups in several South Wales seaports. These have sustained the khat habit and have taught succeeding generations to use it. It is imported regularly by air and stored in domestic deep-freezers without loss of activity.[10]

There are no previous reports of khat-induced optic atrophy in the opthalmological literature, but there was a report of optic neuritis in two khat addicts in Somalia in which vision and optic disc oedema improved after withdrawal of khat.[11]

The two patients described in this report had an unusually high intake over several days. Thereafter they suffered bilateral and rapidly progressive visual deterioration which remained apparently unchanged. Since diet, alcohol, or tobacco intake were unlikely to be causitive, it appears likely that this neurotoxic reaction was a direct result of ingestion of an unusually high dose of khat alkaloids. The reduced ERG in case 1 suggests some retinal toxicity and not merely a toxic optic neuropathy.

Since khat has been used so extensively for many centuries, such reactions must be rare. However, as the plant is now available in the United Kingdom, it should be considered in cases of optic nerve disease in patients of African or Arabian origins.

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Histopathology of mitochondrial cytopathy and the Laurence-Moon-Biedl syndrome

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SUMMARY Clinical and histopathological studies of two patients with distinctly different inherited juvenile retinal dystrophies indicate that the ocular defect in mitochondrial cytopathy involves the underlying pigment epithelium, whereas in the Laurence-Moon-Biedl syndrome the photoreceptor cells are primarily affected

Many retinal dystrophies occur in early childhood, but only a few have known metabolic defects. We present the histopathology of two patients, each representing a specific subcategory of retinal dystrophy. The first is associated with the Kearns-Sayre syndrome (a mitochondrial cytopathy), the second is part of the Laurence-Moon-Biedl syndrome.

The mitochondrial cytopathies (MCs) are progressive disorders affecting many organ systems. The underlying defect appears to be a malfunction within the mitochondria. In skeletal muscle these abnormal mitochondria cluster together giving the appearance of 'ragged red fibres' on light microscopy. When studied by transmission electron microscopy these organelles contain abnormal cristae or crystalline-like inclusion bodies.[1] Histochemistry is a useful adjunct in demonstrating the abnormal mitochondria, whose appearance represents the result of their inability to meet the cell's energy requirements and does not imply a common aetiology.[2] It is likely that MCs are a spectrum of disorders with various mitochondrial or paramitochondrial enzymatic defects. The Kearns-Sayre syndrome is a distinct clinical entity within the spectrum of MCs.

In 1958 Kearns and Sayre described the triad of retinitis pigmentosa, external ophthalmoplegia, and heart block.[3] Affected patients have a great variety of signs and symptoms which include: external ophthalmoplegia (100%), retinal pigmentary degeneration (100%), ptosis (100%), cardiac conduction defects (84%), muscle weakness (77%), cerebellar dysfunction (69%), short stature (63%), and neurosensory hearing loss (54%).[4-7] In MCs there is an abnormal elevation of the cerebrospinal fluid protein. Less commonly, hypoplastic anaemia, impaired renal function, diabetes mellitus, raised serum alanine and creatinine kinase (CK), low serum calcium and parathyroid hormone (PTH), and metabolic acidosis have been reported.

The Laurence-Moon-Biedl syndrome also has retinal manifestations. The classic pentad includes retinal dystrophy (93%), obesity (91%), mental retardation (87%), hypogenitalism (74%), and polydactyly (73%).[9] The full spectrum of clinical features is found in only 40 to 45% of cases,[10] and many incomplete forms have been described. Variability in gene expression and difficulty in detecting some clinical features (obesity, mild mental retardation, and hypogenitalism) in infancy have made clear characterisation of the syndrome difficult in some cases. Renal and upper urinary tract abnormalities are a feature not included in the classic pentad of this syndrome, but reports suggests that these anomalies are common,[11 12] and perhaps urological involvement is a characteristic feature of the syndrome.[11] Alternatively, upper genitourinary tract abnormalities are associated with maldevelopment of the lower tract and may be considered to be an extension of the hypogenitalism.[13-15]

Case reports

CASE 1: MITOCHONDRIAL CYTOPATHY

This girl was born after a 39 weeks normal pregnancy weighing 7 lb 12 oz (3515 g). Her parents were

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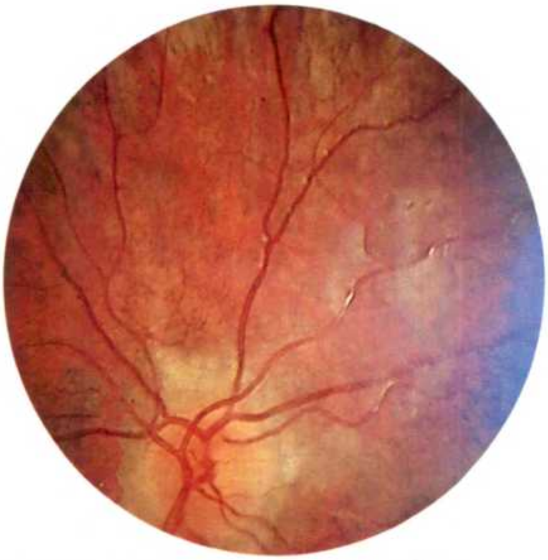

Fig. 1a *The ocular fundus in case 1 (Kearns-Sayre syndrome), showing a relatively normal appearing posterior pole.*

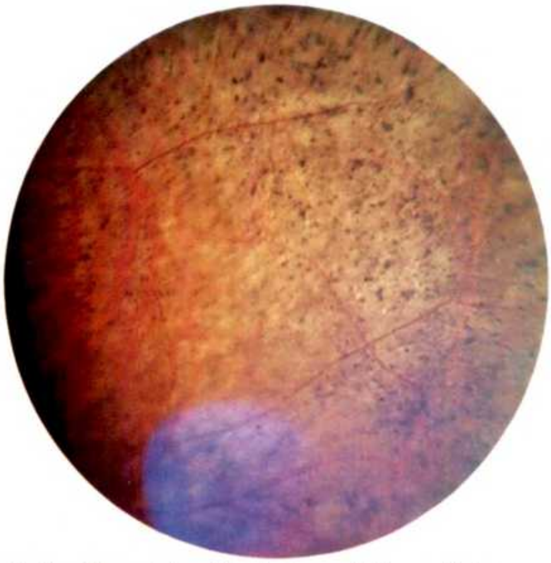

Fig 1b *The peripheral fundus in case 1 (Kearns-Sayre syndrome). Note the salt-and-pepper pigmentation. Both fundus photographs were taken at 9 years 3 months of age.*

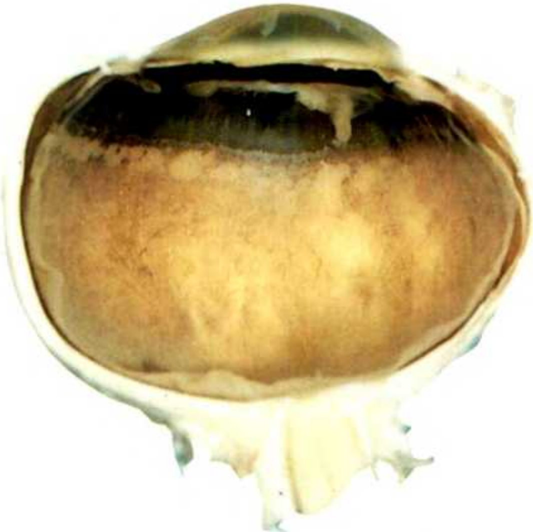

Fig. 1c *The hemisected globe in case 1, which clearly shows the discontinuous salt-and-pepper pigmentation.*

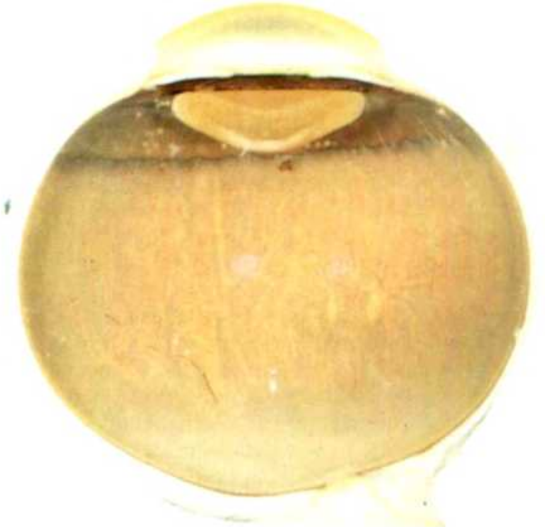

Fig. 1d *The hemisected globe in case 2, which appears normal.*

healthy and not consanguineous. She had two normal siblings, and there was no significant family history. She was healthy until 8 months old, when she was noted to be pale and was found to have prednisolone responsive red cell hypoplasia. From 4½ years she failed to thrive, with height and weight falling to less than the 3rd percentile.

Renal failure was diagnosed at 9½ years and a renal biopsy performed at 9¾ years was suggestive of juvenile nephronophthisis. Subsequently she required dialysis, and at 11½ years a renal transplant was performed. Soon afterwards she developed insulin dependent diabetes mellitus possibly related to steroid therapy.

She required spectacles from an early age for hypermetropic astigmatism. A pigmentary retinopathy was first noted at 9½ years (Figs. 1a and 1b); her visual acuity was then 6/9 in both eyes, extraocular movements were full, colour vision (Ishihara plates) was normal, but the visual fields were constricted. Both electroretinogram (ERG) and visual evoked cortical response (VER) by means of an averaged skin electrode technique to flash stimuli, were normal. At age 12 years posterior subcapsular cataracts were noted, and her visual acuity had decreased to 6/24; she had a nearly complete external ophthalmoplegia. By 12½ years the acuity was 3/36 and a left lensectomy was performed, which improved the acuity to 6/36.

She had a few seizures beginning at 9¾ years. A seizure at 11 years resulted in a marked exaggeration of her ataxia and poor vision and hearing, but she returned to her preseizure state after about one week. Her seventh and final seizure occurred at age 12 years, at six weeks before her death. A CT scan performed at 11 years 10 months of age showed cerebellar and cerebral atrophy.

From 10 years of age she had a variable ataxia and by 11½ years she required support to walk; a generalised myopathy was also then apparent with normal sensory and motor nerve conduction. At 12 years she had a myopathic facies, marked ptosis, generalised muscle wasting (especially the quadriceps), proximal limb weakness, generalised hyporeflexia, with flexor plantar responses, normal tone and sensation, broad based gait, poor co-ordination, and scanning dysarthria.

A muscle biopsy at 12 years showed numerous ragged red fibres with excess glycogen and fat.

Hearing loss started at 4 years, high frequency sensorineural deafness was moderately severe by 12 years.

Cardiac failure first occurred at 12¾ years due to a dilated, poorly functioning left ventricle, which was compatible with a cardiomyopathy. The electrocardiogram progessively demonstrated left axis deviation, left bundle branch block, and left anterior hemiblock. At 12¾ years she died of intractable cardiac failure precipitated by viral pneumonia.

Investigations

These showed a hypochromic normocytic anaemia, raised cerebrospinal fluid (CSF) protein (1000 mg/1); low serum parathormone (PTH) (50, 90, and 120 ng/l), and creatine kinase at the upper limit of normal (60 IU/1). Alanine was noted in her urine, and she showed a corrected metabolic acidosis with low calcium and high phosphate.

Necropsy results

She had pneumonitis, and the heart was moderately enlarged and dilated with a pale myocardium. The liver showed fatty changes, and the kidneys were atrophic but otherwise appeared normal. The adrenals were atrophic.

Histological preparations showed a viral pneumonia, signs of cardiomyopathy, and the kidneys showed tubular atrophy with relative preservation of the glomeruli. There was Purkinje cell degeneration in the cerebellum.

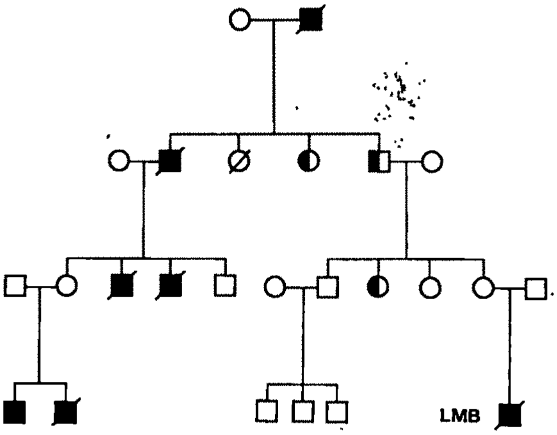

Fig. 2 *Family tree of case number two. Squares, males; circles, females; open symbols, unaffected or not known to be affected; solid symbols, chronic renal failure with or without proved renal dys- or agenesis, half-closed symbols, duplex kidneys; slash through symbols, deceased.* LMB=*Laurence-Moon-Biedl syndrome.*

CASE 2: LAURENCE-MOON-BIEDL SYNDROME

This boy was born weighing 8 lb 3 oz (3714 g) after a normal pregnancy to healthy non-consanguineous parents. His mother's family had an extensive history of renal disease (Fig. 2). He was normal apart from postaxial polydactyly of both feet. He required one month to regain his birth weight and at six months was investigated for failure to thrive; he weighed 6·5 kg (3rd percentile) with a height of 64·5 cm (just below the 10th percentile). He was in renal failure with plasma creatinine 213 µmol/l and urea 15·9 mmol/l, and the glomerular filtration rate (GFR) was 11 ml/min/1·73 m surface area. The intravenous pyelogram (IVP) and cystogram were normal. The renal ultrasound suggested parenchymal cysts. Over the next 3½ years his renal function gradually deteriorated, and at nearly 4 years peritoneal dialysis was started. He received a renal transplant, followed by several episodes of graft rejection requiring high doses of methylprednisolone and antilymphocyte globulin, during which time he was hyponatraemic, hypertensive, and had three epileptic seizures. Pneumonia and pancytopenia developed, and death occurred at four years one month.

At nine months of age clinical assessment showed only a minimal hypermetropic astigmatism, but at 10 months he tended to screw up his eyes in bright light and at 13 months he developed occasional jerky horizontal nystagmus. The left fundus was seen clearly and was ophthalmoscopically normal. At 14 months he had constant, variable-amplitude, high-frequency horizontal nystagmus. An examination under anaesthetic (EUA) at 14½ months showed both eyes to be hypermetropic (+5·00 R and L), with normal fundi. The ERG was abnormal, with scotopic responses markedly subnormal. The photopic responses to flicker were reduced in amplitude. By two years he had poor vision, especially at night, and coarse nystagmus. An EUA at 2¼ years showed pale discs, attenuated vessels, exposed choroidal vessels, and scattered hyperpigmentation; the ERG was unrecordable. At 4 years old he had bilateral posterior subcapsular cataracts and grossly dystrophic fundi.

A developmental assessment at 2 years 9 months showed motor development delay to the 2-year level, but language comprehension was normal, and there was marked expressive language delay. Hearing was normal.

From 2¾ years he was clumsy, with mild ataxia of both upper limbs and a broad based gait.

Investigations

He had a normocytic hypochromic anaemia and the plasma levels of creatinine ranged from 215 to 721 µmol/l and those of urea from 22 to 47 mmol/l, with a GFR of 11 to 5·8 ml/min/1·73 m surface area. Bone age was delayed, with renal osteodystrophy, and he was hypocalcaemic and hyperphosphataemic, with an alkaline phosphatase of over 1000 IU/l. Parathyroid hormone levels were up to 2610 ng/l. There was a persistent compensated metabolic acidosis. Electro- and echocardiograms were normal.

Necropsy

The heart was large, with hypertrophy of the ventricular walls. The kidneys were small, dysplastic, and showed nodularity with numerous cysts. The testes were of normal size, and there was no abnormality of the external genitalia. He had bronchopenumonia.

Histological preparation of ocular tissue

The time from death to enucleation was several hours in case 1 but less than one hour in case 2. A penetrating incision was made of the ora serrata, and the eyes were fixed in 2·5% glutaraldehyde buffered in 0·2 M sodium cacodylate, containing 10 mg/ml calcium chloride, with a final pH of 7·4. After overnight fixation the eyes were hemisected and macrophotographs were taken of their posterior portions.

Samples were taken from the hemisected globes under a dissecting microscope. The specimens were obtained on a horizontal axis from ora to ora through the macula, and vertically from ora to ora through the optic disc, their location, orientation, and relationship to the other samples being recorded so that they could be determined even after being embedded in plastic. The isolated samples were postfixed for one hour in 1% osmium tetroxide buffered in 0·1 M sodium cacodylate before being dehydrated in a series of ascending concentrations of ethanol in water, and embedded in Araldite (CY212) via epoxypropane. Sections for light microscopy were cut on glass knives and stained with toluidine blue. Ultrathin sections were cut on diamond knives, mounted on uncoated copper grids, stained with uranyl acetate and lead citrate, and examined with an AEI 801 electron microscope.

One eye from each case was processed for tissue culture. This was successful from case 2, and studies of pigment epithelial cell behaviour have been undertaken.[16-18]

Results

Neither globe had a macroscopic bone spicule zone.

In case 1 the fundus was pale, with blotchy and discontinuous pigmentation, most dense at the posterior pole and in the far periphery (Fig. 1c), where the pigment was present in both the pigment epithelium (RPE) and the choroid. In the far periphery there were a number of lesions of variable size and shape in which there was a sharply demarcated loss of RPE cells, which reduced the pigment epithelium to a number of random isthmus-like projections of cells, extending centrally from the ora.

In case 2 the hemisected globe looked normal (Fig. 1d).

CASE I

Histology

In case 1 there was diffuse and even cell loss in the neural retina, with sectorial disease in the pigment epithelium.

In the macula (Fig. 3a) and far periphery (Fig. 3b) the surviving RPE cells were compressed apicobasally, with sparse amounts of melanin. In the mid periphery there were small focal areas of isolated pigmented cells (Fig. 3c, d) between which the denuded surface of Bruch's membrane was either directly exposed to the remnants of the interphotoreceptor matrix or recolonised by one or more layers of amelanotic cells (Fig. 4a). In a few areas where

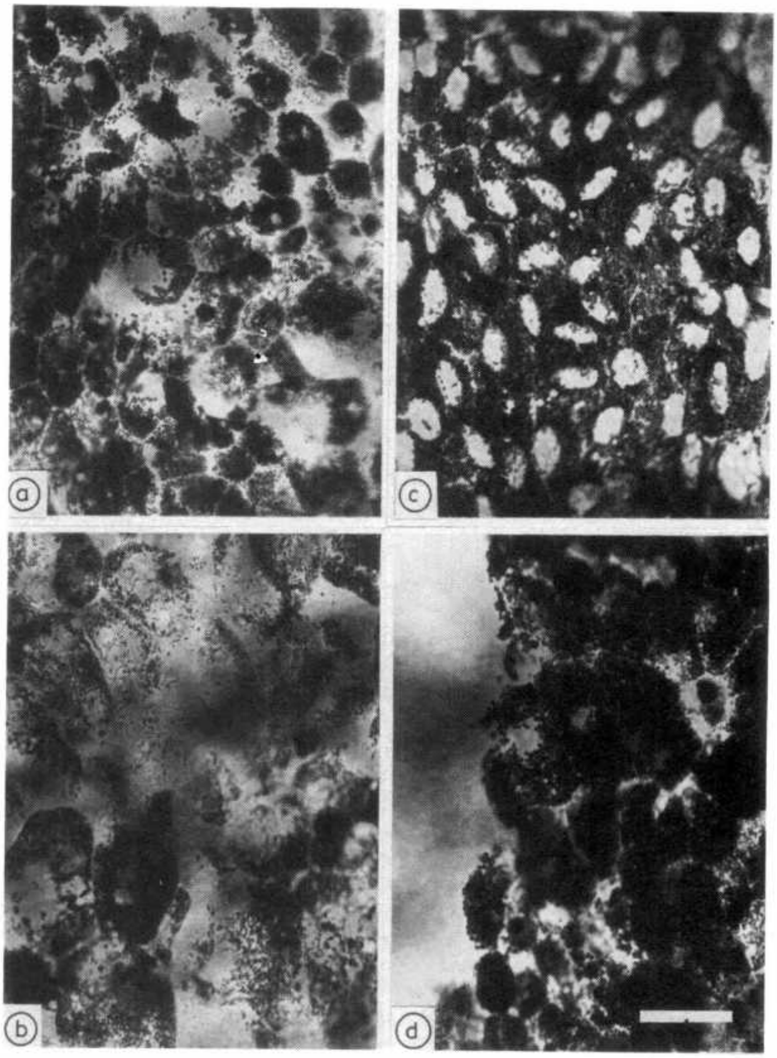

Fig. 3 *Light micrographs of wholemount preparations of retinal pigment epithelial cells from a variety of locations in the Kearns-Sayre syndrome eye.* (a) *Macula.* (b) *Far periphery.* (c), (d) *Mid periphery. Note that the cells are highly irregular in shape and vary in size. In the mid periphery, focal areas of cell loss result in lesions with sharply defined borders. Scale=50 µm.*

neural retinal cells dipped towards Bruch's membrane, glial proliferation resulted in direct apposition of glial elements with Bruch's membrane. Beneath areas of pigment epithelial cell loss there was also a relative loss of the innermost elements of the choriocapillaris (Fig. 4b). In regions of vessel loss there was no down growth and expansion of columns of Bruch's membrane, as occurs in the elderly, but invasion of fibroblasts and the production of collagen.

All the photoreceptor cells were in a very poor condition (Fig. 5). At the fovea there was a complete loss of photoreceptor cell outer segments, and reduced numbers of cone cell remnants, shown by counting nuclei, which extended into the mid periphery, where both inner and outer segments were absent. In most other conditions, while rod cells degenerate leaving no vestiges, remnants of cone cells may remain for many years, particularly the nucleus and truncated inner segments. Towards the margins of the mid peripheral zone, occasional remnants of inner and outer segments of photoreceptor cells were seen which were always adjacent to islands of pigment epithelial cells; the inner segments were shrunken and stained intensely, while the outer segments were tiny vestiges.

In the space formerly occupied by the interphotoreceptor matrix were numerous spherical lipid droplets of varying diameters and staining properties (Fig. 5b). Some were associated with the apical layer of the pigment epithelium, while in other areas they were

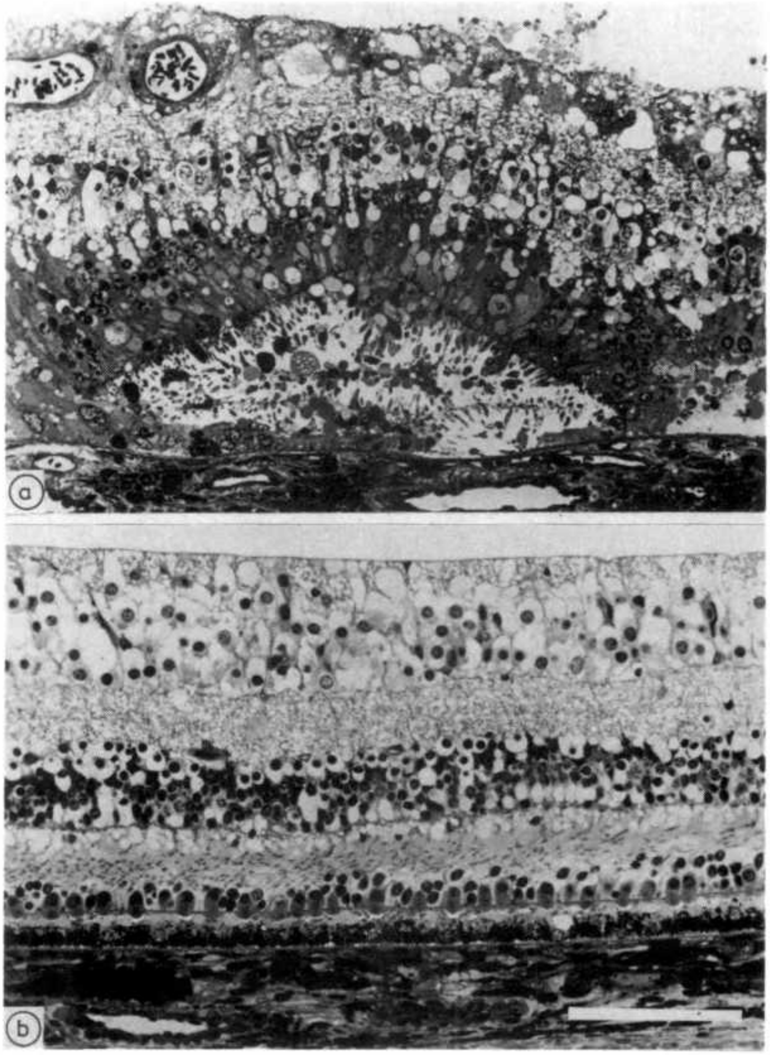

Fig. 4 *Light micrographs of retinae of* (a) *the Kearn-Sayre syndrome and* (b) *the Laurence-Moon-Biedl case.* (a) *An area of mid peripheral retina is illustrated with a central region of partially degenerate photoreceptor cells with recognisable inner segments.* (b) *A representative section of macular retina showing good preservation of the inner retina but a loss of the outer segments of the photoreceptor cells. The 'rounded up' inner segments and nuclei of some affected cones make them particularly prominent. Scale=100 μm.*

adjacent to Bruch's membrane. They appeared to represent extracellular accumulations of breakdown products of the outer segment membranes of photoreceptor cells. They were unlike the autolytic debris from long term post-mortem material.

Post-mortem changes in the inner retina showed as areas of vacuolation and oedema in the plexiform layers and pyknosis in the nuclear layers. There was no evidence of trans-synaptic degeneration, and with the exception of pigment epithelium and photoreceptor cells all retinal layers were well preserved, as was the retinal capillary bed.

Ultrastructure

The post-mortem changes made ultrastructural analysis difficult except on the outer retinal components.

The remaining RPE cells had a primitive appearance, having lost many organelles including melanin granules and lipofuscin (Fig. 6a). Adjacent to photoreceptor cell vestiges there were no phagosomes, and here there were occasional extracellular aggregations of outer segment material associated with the apical membranes of epithelial cells. Commonly there was a reduction in the numbers and complexity of mitochondria in these cells, and unlike in normal cells these few mitochondria were diffuse throughout the cytoplasm. There was a widespread reduction in cell membrane complexity, with loss of apical villi and basal convolutions. Some cells had elaborate arrays

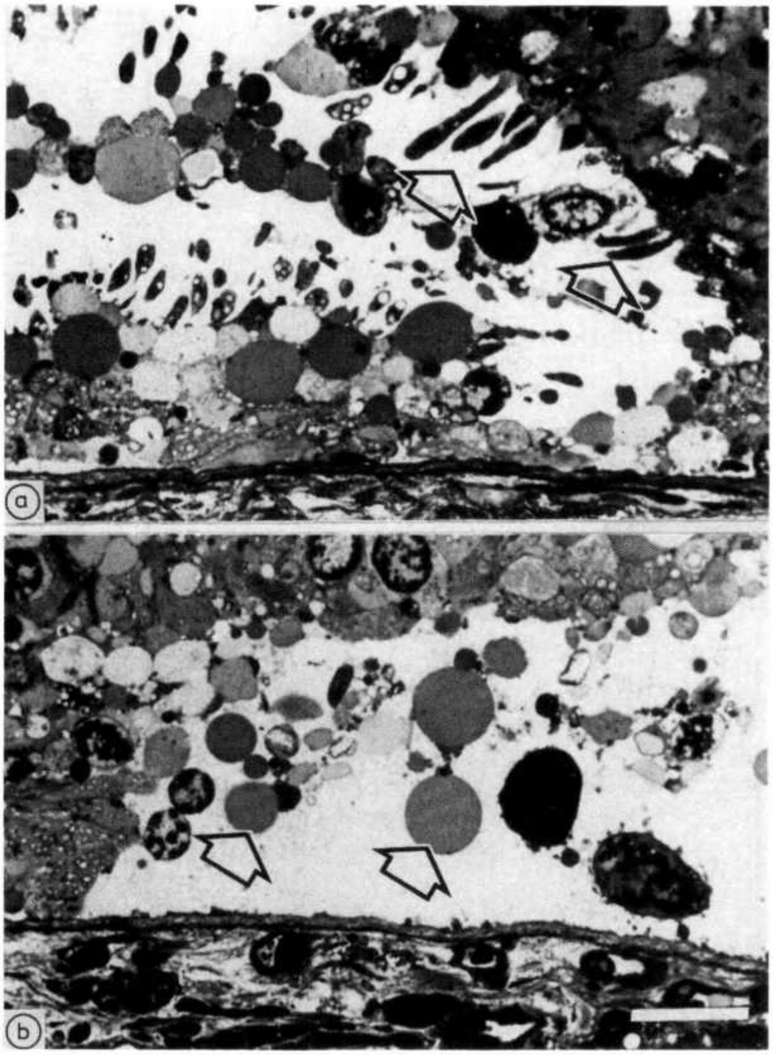

Fig. 5 *Light micrographs of the outer retina and inner choroid in the mid peripheral region of the Kearn-Sayre eye. In both regions bare areas of Bruch's membrane are seen, and the choriocapillaris is sparse.* (a) *Remnants of photoreceptor inner and outer segments (arrowed) were rare and their distribution was not correlated with presence or absence of pigment epithelial cells.* (b) *An area where the outer components of the photoreceptor cells were absent and subretinal lipid globules (arrowed) and macrophages were apparent in the subretinal space. Scale=25 µm.*

of cytoskeletal elements or filaments, similar to those that developed in tissue cultures. This may be related to the migratory activity of epithelial cells freed from contact inhibition.

Bruch's membrane contained more membranous debris than is normally expected at this age, and its basement membrane component from the pigment epithelium was poorly developed.

Where there were vestiges of inner and outer segments of photoreceptor cells, they were grossly abnormal, and in the inner segments of both rods and cones there were fewer organelles. The remaining mitochondria were shrunken, with densely staining membranes and atypical cristae (Fig. 6b). They did not show the same ultrastructure as the mitochondria of skeletal muscle in mitochondrial cytopathy. The cristae of the photoreceptor cells were swollen and densely packed with a vesicular appearance, without multilayering of cristae or crystal-like inclusions. This is unusual and significant, because the inner segments of photoreceptor cells contain more mitochondria than any other cell. All inner segments contained many autophagic vacuoles of differing morphologies.

The remnants of the rod and cone outer segments were morphologically dissimilar. Most cone outer segments were tiny vestiges, some 2 to 5 µm long, with randomised and disorientated vesicular arrays of membranes (Fig. 6c), but a few had degenerated further, and no internal membranes were present and

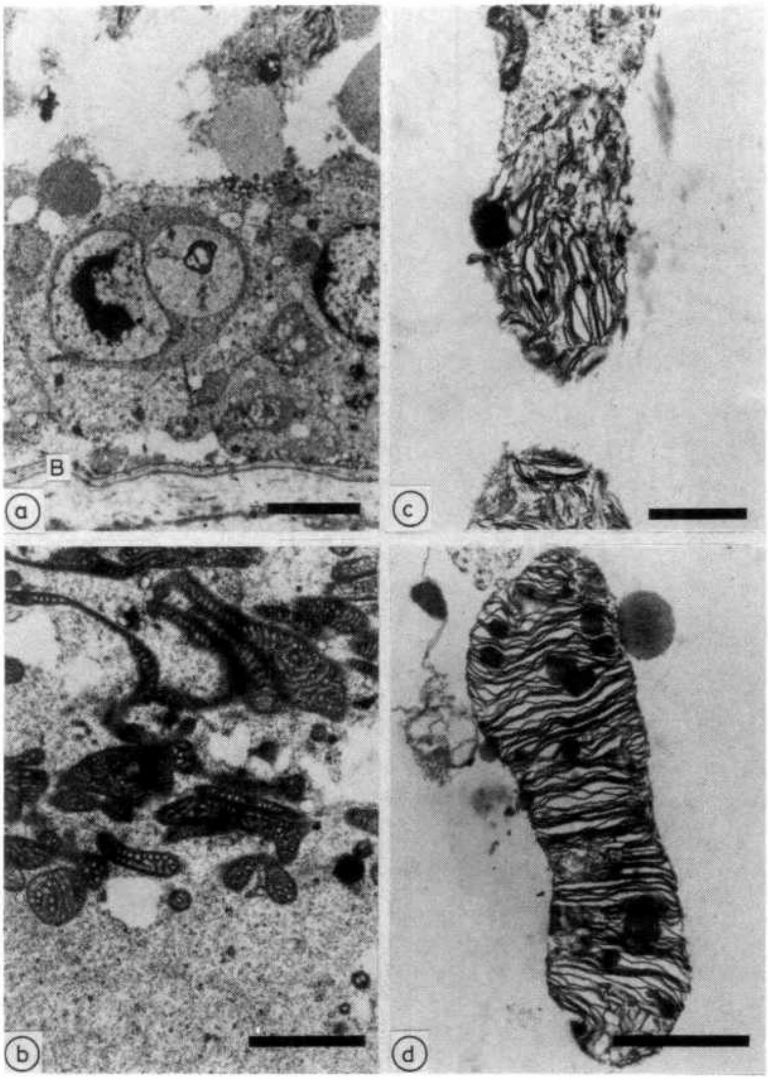

Fig. 6 *Representative electron micrographs of a variety of retinal locations in the Kearns-Sayre syndrome eye.* (a) *An area of Bruch's membrane* (B) *covered by atypical amelanotic cells which have a very poorly developed basement membrane. The apical membranes of these cells were never complex or seen to exhibit apical villi, and the subretinal space was enlarged.* (b) *The outer edge of the ellipsoid of a cone remnant showing the presence of slightly shrunken and atypical mitochondria but also demonstrating that they do not have the architecture frequently seen in such organelles in mitochondrial cytopathies.* (c) *View of the ciliary region of a photoreceptor cell remnant showing the disorganisation and disorientation of outer segment disc membranes.* (d) *Shows the peculiar lipid globule inclusions seen in some surviving photoreceptor cell outer segments. Scales are* (a) *3* µ*m;* (b) *2* µ*m;* (c) *1* µ*m; (d)* 2 µ*m.*

the boundary membrane contained a homogeneous granular mass. The remains of rod outer segments were longer, up to 10 µm, and frequently contained small regions of organised disc membranes. They also showed globular lipid-like inclusions within the membrane stacks of their outer segments and associated with their boundary membranes (Fig. 6d). In areas where rod outer segments were short or absent, there were huge extracellular globules with amorphous or granular staining.

CASE 2

Histology

Case 2 showed regional differences in retinal morphology, with the severest changes at the macula, and progressively less marked peripherally (Fig. 4b).

The RPE was relatively normal macroscopically, but on section it had relatively few melanin granules and was full of lipofuscin (Fig. 7). The loss of melanin was most marked at the macula, where there were few intracellular pigment granules. The lipofuscin content in cells was higher than age matched controls, being comparable to those in 20- to 30-year-olds. The general morphology of RPE cells everywhere appeared relatively normal except for a slight increase in apico-basal dimensions; there were no focal lesions or areas of cell loss.

Photoreceptor cell loss was most marked centrally (Fig. 7a), where the foveal cell population was reduced by death and atrophy, with the remaining

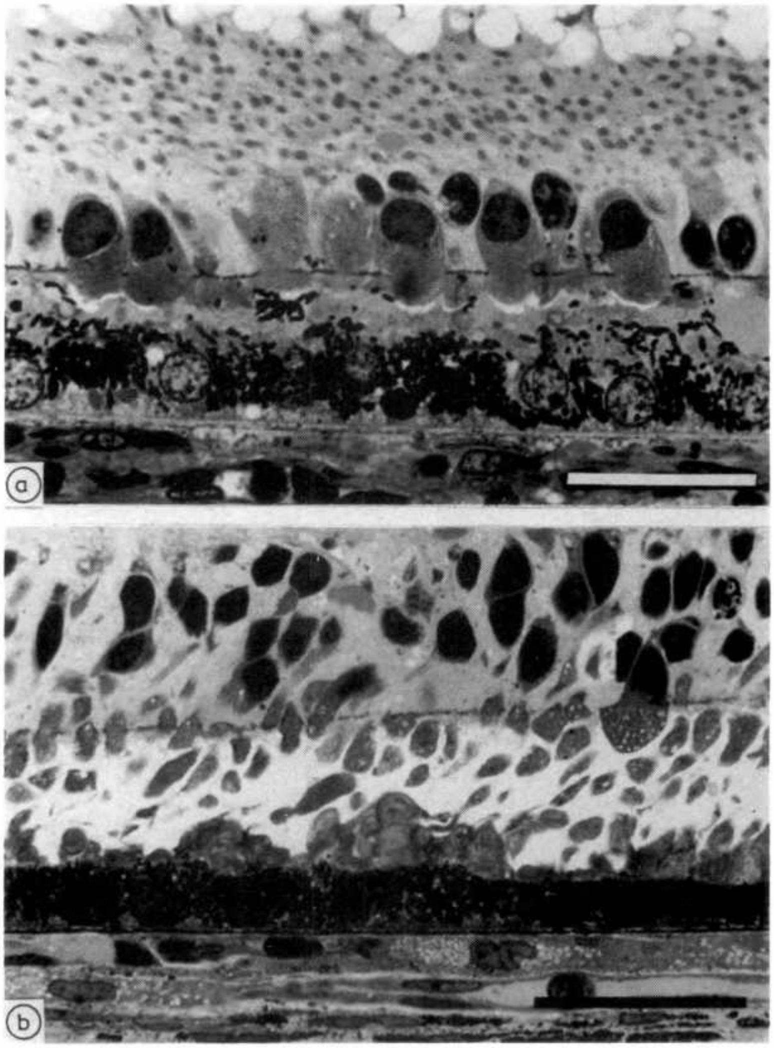

Fig. 7 *Light micrographs of* (a) *the macula and* (b) *the mid peripheral retina in the Laurence-Moon-Biedl case.* (a) *Shows a total loss of rod cells and the absence of any outer segment material. Some rounded cone cell remnants are present and the pigment epithelium contains an abnormally high concentration of lipofuscin.* (b) *Shows remnants of both rod and cone cells with outer segment debris adjacent to the apical membrane of the retinal pigment epithelium. Scales are* (a) *20 µm;* (b) *30 µm.*

cells losing their outer segments and with their inner segments swollen to the size of those in 60–70-year-old normal persons. The macular outer segments were absent, and rounded inner segments were seen abutted to the pigment epithelium. The cell remnants distorted the outer limiting membrane, making it more prominent, which emphasised the interphotoreceptor matrix. In the mid periphery photoreceptor outer segments of both rods and cones were only half their normal length, and their tips were extremely disorientated at the surface of the pigment epithelium, with an appearance similar to that of the Royal College of Surgeons' rat[19] (Fig. 7b).

The inner retinal layers were well preserved except at the macula, where there was a reduction in the number of ganglion cells.

Ultrastructure

The difference in morphology between central and mid peripheral areas was emphasised on electron microscopy.

The central RPE cells contained a variety of densely staining inclusions, including lipofuscin granules, melanolysosomes and melanolipofuscin (Fig. 8a), of various shapes and sizes often associated with lysosomes or microperoxisomes. By reducing available cell volume the waste products reduced the number of active organelles, including mitochondria. Both the apical and basal membranes of the RPE had

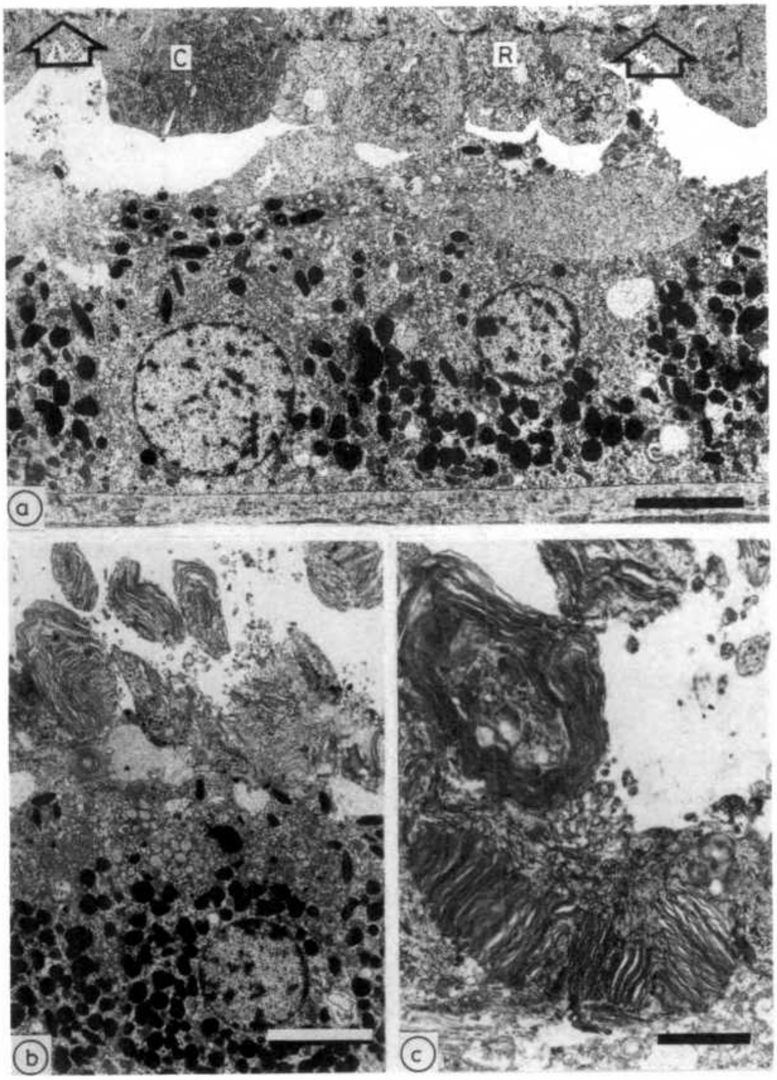

Fig. 8 *Electron micrographs of various locations in the retina of the Laurence-Moon-Biedl case.* (a) *Micrograph to demonstrate the total absence of outer segment material at the macula. The pigment epithelial cells have lost their convoluted basal border and contain abnormally large amounts of lipofuscin. Remnants of both rod* (R) *and cone* (C) *inner segments can be seen projecting through the outer limiting membrane (arrowed).* (b, c) *Micrographs to show the disorganised nature of the extracellular debris of photoreceptor outer segments adjacent to the apical membrane of the retinal pigment epithelium. Scales are* (a) *and* (b) *5 μm;* (c) *2 μm.*

a simple configuration, with the loss of mircrovilli and basal convolutions.

Apart from a reduced basement membrane in relation to the RPE, Bruch's membrane and the choriocapillaris were normal.

In the mid periphery, where subretinal debris was seen with the light microscope, the RPE cells showed similar abnormalities to their central counterparts, but with more organelles. Their apical membranes lacked microvilli, and there were sheets or whirls of membranes of photoreceptor cell outer segments (Fig. 8b), which were extracellular, and where they were deep to the surface of the RPE they occupied a distended extracellular space between the lateral margins of adjacent cells (Fig. 8c). There were no short-term phagosomes in the cytoplasm of the RPE cells, but huge amounts of lipofuscin, melanoloysosomes, and melanolipofuscin were present, indicating recent phagocytic activity.

The neuroretinal-RPE interface varied throughout the retina because of variable loss of photoreceptor cells. Centrally, 'fat' vestigial cone inner segments were either opposed to the apical surface of the RPE, or were separated from it by tiny deposits of interphotoreceptor matrix. Here the outer limiting membrane was within 20 μm of Bruch's membrane, and, unlike situations where disease results in loss of photoreceptor cells, there was no proliferation of glial elements external to the outer limiting membrane. Extensive villus-like processes from the outer-

Table 1 *Comparison of the clinical features of the Kearns-Sayre and Laurence-Moon-Biedl syndromes*

	K-S	*Case 1*	*L-M-B*	*Case 2*
Eye features				
Poor visual acuity		6/36	Common	6/36
and/or night vision	40%	No	Common	Yes
Ptosis and/or external ophthalmoplegia	100%	Yes	Reported	No
Nystagmus	Not reported	No	Common	Yes
Constricted fields	Reported	Yes	Common	Not known
Corneal opacities	5–11%	No	Not reported	No
Cataracts	Reported	Yes	Reported	Yes
Pale discs	Reported (rare)	No	Reported	Yes
Attenuated vessels	Reported (rare)	No	Reported	Yes
Maculopathy	Reported (rare)	No	Reported	No
Abnormal retinal pigment	100%	Yes	79%	Yes
Abnormal ERG	Common	Normal	Common	Flat
Abnormal VER	Common	Normal	Common	Not done
Neurological features				
Impaired intellect	32–64%	No	87%	Yes
Seizure disorder	Reported (rare)	Yes	Reported (rare)	No
Auditory dysfunction	47–79%	Yes	Reported	No
Vestibular dysfunction	77–85%	Not assessed	Not reported	No
Muscle: weakness	63–80%	Yes	Reported (rare)	No
Wasting	Reported	Yes	Reported (rare)	No
Abnormal reflexes	decreased (40%)	Decreased	Reported (rare)	Normal
Abnormal tone	Reported (hypo)	Normal	Reported (rare)	Normal
Cerebellar dysfunction	63–69%	Marked	Reported (rare)	Mild
Abnormal EEG	Common	Yes	Common	Not done
CT scan (atrophy)	Reported	Yes	Not reported	Not done
Spongy degeneration (CNS)	Reported	Not reported	Not reported	No
General features				
Failure to thrive	Common	Marked	Not reported	No
Obesity	Not reported	No	91%	No
Short stature	78%	Yes	Reported (rare)	No
Delayed bone age	Common	Yes	Reported (rare)	Not done
Hypoplastic teeth	Reported	Yes	Not reported	Not known
Polydactyly	Not reported	No	73%	Yes
Cardiac conduction defect	84–100%	Yes	Not reported	No
Cardiomyopathy	Reported	Yes	Reported (rare)	No
Confenital heart disease	Not reported	No	Common	No
Chronic renal failure	Reported	Yes	Common	Yes
Genitourinary anomaly	Reported	Yes	74%	Yes
Laboratory investigations				
Ragged-red fibres	Common	Yes	Not reported	Not done
Abnormal mitochondria (EM)	Common	No EM	Not reported	Not done
Elevated CSF protein	74–100%	Yes	Not reported	Not done
Elevated pyruvate/lactate	Common	Not done	Not reported	Not done
Elevated CK	Common	Yes	Not reported	Not done
Anaemia	Reported	Yes	Reported	Yes
Serum amino acids	(+Ala) reported	Not done	(+ branched chain and arg.) reported	Not done
Amino aciduria	Not reported	(+) ala.	Not reported	(+) gly.
Hypoparathyroidism	12%	Yes	Not reported	No
Elevated blood glucose	Reported	Yes	Reported (rare)	No

most aspects of Müller's fibres were prominent only where photoreceptor cell outer segments were present.

Cone remnants in the central retina displayed a remarkably similar ultrastructure, showing a reduction in the ellipsoid mitochondrial content and a dissolution of the myoid region of the inner segment, with a commensurate loss of Golgi bodies and lysosomes. In most cells in this region there were polymorphic autophagic vacuoles. Both the inner and outer connecting fibres of these residual cones were easy to identify because of the simplicity of the outer nuclear layer resulting from atrophy of a significant number of cells. Remaining synaptic pedicles in the outer plexiform layer were enlarged, but were simplified with reduced synaptic contacts.

In the mid peripheral zone short disorganised outer segments were related to both rods and cones, and their discs were misaligned with membranes at right angles to their normal axis, often fused to form vesiculate and tubular arrays. As these very short and disorganised outer segments terminated in the extracellular membrane sheets at the apical surface of the RPE, it was difficult to discriminate between inter- and intracellular membrane systems, and their length could not be measured. The length of the outer segments increased with their distance from the macula. Mid peripheral cone inner segments showed similar changes to those in the central region with reduced numbers of organelles but with more autophagic vacuoles.

Discussion

The diagnosis of mitochondrial cytopathy in the first case study was made by using Kearns and Sayre's[3] original criteria and those of subsequent studies.[5 8 20 21]

Fundal changes in mitochondrial cytopathy range from fine granular salt-and-pepper pigmentation to a 'moth-eaten' appearance, though they are sometimes described as 'atypical retinitis pigmentosa.' The defects leading to this retinal degeneration are unknown. However, abnormal mitochondria have been found in biopsies of various other tissues and occur most frequently in skeletal muscle, but have also been observed in liver,[1] cerebellum,[22], heart,[23] skin,[21] and smooth muscle.[24] Histochemistry also shows a mitochondrial defect by demonstating altered mitochondrial enzyme activity,[8] with a decrease in cytochrome oxidase activity and an increase in that of succinate dehydrogenase.[25 26]

There are 10 reports on ocular histopathology; two papers report the same cases. Therefore the total data are five histological reports and three accounts of ultrastructure.[3 27-34] The consistent histological picture is of marked atrophy and degeneration of the outer retinal layers and RPE but preservation of the ganglion cell and nerve fibre layers. Our case 1 conforms to this morphological pattern with generalised loss of the outer retina and preservation of the inner retinal layers. The loss of vessels in the choriocapillaris in our young patient was significant, and like Sarks[35] we believe that as retinal cells die the choriocapillaris atrophies secondarily to reduced metabolic demand. The mitochondria in the preserved areas of the inner segment were shrunken, with atypical electron dense membranes and abnormal arrays of cristae.

Given the ambiguities in the clinical diagnosis of mitochondrial cytopathy, the range of presenting symptoms, and the age range of the small number of patients with ocular histological studies, the variation between the cases is not surprising. Histopathology is a spatial analysis of temporal processes, and the superimposition of one spectrum (time) on a second spectrum (genetic variability) complicates direct comparison. Some useful generalisations can be made. Characteristically abnormal mitochondria are not found in ocular tissues. Mitochondria from non-ocular tissues in mitochondrial cytopathies are misshapen, with concentric cristae or paracrystalline inclusions,[5 36-42] and they are so frequent in the skeletal muscles that they may give rise to the 'ragged red fibres' seen on microscopy. Ragged red fibres were present in skeletal muscles of our patient but not in extraocular muscle. These abnormal organelles and the multisystem degenerations in these inherited disorders suggest that the genetic defects are primarily expressed in aberrant mitochondrial function.[37] All inherited diseases are phenotypically expressed in aberrant biochemistry. In the mitochondrial cytopathies, if the biochemical lesions are present in all mitochondria, then their actions must proceed at different rates in different sites, but everywhere they must be at least normal enough for survival. In the inherited dystrophies the genetic lesions show during early life and perhaps reflect the progressive failure of repair mechanisms of aging.

Mitochondria have been examined in retinal tissues, but changes similar to those described systemically have not been identified, though enlarged mitochondria within the retinal pigment epithelium have been described[31 43]; these authors concede that the changes may be due to post-mortem autolysis. In a study of a 14-year-old patient with the Kearns-Sayre syndrome large numbers of enlarged mitochondria within the retinal pigment epithelium were implicated in photoreceptor cell loss[34] by their disturbing the energy relationships required for homoeostasis of visual cells.[44] The argument here is that mitochondrial proliferation is a compensation for reduction in efficiency, which in turn results in changes in dependent cells. Such a causal relationship is uncertain, but from the morphological evidence in both the McKechnie report[34] and our study it could equally be argued that the mitochondrial changes are secondary to failure of transepithelial transport with reduced exchange area, that is, the loss of convolutions on the basal membrane of the remaining pigment epithelial cells.

Whatever the primary mechanism, we support McKechnie *et al.*[34] and Eagle *et al.*,[31] who consider that the genetic defect is first expressed in the RPE and that photoreceptor cell losses are secondary. Our conclusions are based on these related observations.

(1) Photoreceptor cells were absent where RPE cells were absent.

(2) The shape of photoreceptor cell remnants closely followed the degree of atrophic changes within adjacent RPE cells.

(3) There was very little invasion of RPE cells into the neural retina in the 'bone spicule zone.'

(4) There was significant loss of choroidal capillaries in areas of RPE cell loss.

The role of the RPE in photoreceptor cell maintenance means that a malfunction in any one of a number of interrelated processes could result in photoreceptor cell death.[44] Animal studies show that in some inherited retinal dystrophies the defective gene action is expressed solely within the RPE cells.[45 46] In our study the RPE lesions have sharply defined edges, while the overlying photoreceptor cells have more graded changes. The large amounts of unphagocytosed subretinal lipids near residual photoreceptors indicate a malfunction in the underlying RPE cells. Both aspects of photoreceptor damage distribution suggest a primary malfunction within the pigment cells, with a secondary involvement of dependent cells, a phenomenon suspected in gyrate atrophy.[47] This concept is further supported by the lack of pigmented cells in the neural retina. Where photoreceptor cells are lost in the presence of RPE cells the latter become migratory. Atrophy of RPE cells results in windows enabling the choroid to be seen ophthalmoscopically. The depletion of RPE with the absence of pigmented cells in the neural retina results in the 'salt-and-pepper' fundus. The loss of choroidal capillaries is usually in conditions in which severe changes occur in the RPE rather than in the photoreceptor cells.[35]

The diagnosis of the Laurence-Moon-Biedl syndrome in the second case was made on the basis of the retinal dystrophy, postaxial polydactyly, and mild mental retardation. Two of the five cardinal features of the Laurence-Moon-Biedl syndrome, obesity and hypogenitalism, were absent, but obesity and hypogenitalism are often difficult to diagnose in early childhood.[9 10 48 49] Our patient's mother strictly controlled his diet, thereby limiting his weight.

Chronic renal failure was the presenting feature, and the strong family history of renal disease is therefore of interest (Fig. 2). Several members of our patient's family, although asymptomatic, were found to have unilateral duplex kidneys when investigated by ultrasound. There is increasing evidence that renal and genitourinary tract anomalies are much more common in this syndrome than previously recognised.[11 12 50-54] The majority of necropsies of the Laurence-Moon-Biedl syndrome report a genitourinary tract abnormality, and in one series uraemia was the commonest cause of death.[11 49]

Patients with the Laurence-Moon-Biedl syndrome commonly present with nystagmus, failing vision, and night blindness.[9] The ERG is always abnormal. Funduscopy may be normal early in the disease, but a retinal degeneration almost always develops,[55] being present in 93% of cases.[10] 'Typical' retinitis pigmentosa is found in only 15 to 20% of cases,[56] while in the majority pigmentary changes are 'atypical.' Various morphologies, described as a diffuse pigmentary retinopathy, retinitis pigmentosa sine pigmento, retinitis punctata albescens, other forms of tapetoretinal degeneration, and pigmentary retinopathy of undetermined type together with choroidal and macular degenerations, have been observed. This heterogeneity may be due either to a spectrum of disease within the syndrome or to describing patients at different points of development in the disease.

Most reports of ocular histopathology have been on patients over 18 years of age.[56-61] Usually they are described as having advanced retinal degeneration with loss of rods, cones, and outer and inner nuclear layers, reduction of the ganglion cell layer with glial proliferation and degeneration, and proliferation of the RPE. Most of the eyes had little or no vision and must be regarded as being at the end stage of a retinal degeneration. When McLoughlin and Shanklin[62] examined their two patients with the Laurence-Moon-Biedl syndrome they found no abnormalities grossly or histologically. Their patients were three months and five years of age respectively and therefore may not have had time to develop the pigmentary retinopathy.

In contrast to case 1, the histopathology of the outer retina in case 2 showed photoreceptor cell degeneration without significant changes in the RPE. The underlying mechanisms are as obscure as the reason for the distribution of the lesions with severest degeneration at the macula. The disease in this eye affected photoreceptor cells selectively, without discrimination between rods or cones. The macular changes probably reflect a complex regional differentiation rather than the selective loss of cone cells.

The lipofuscin and other granular inclusions within the RPE cells indicate one or more of the following: (1) these cells have had a prolonged phagocytic load; (2) they have had an excessive load recently; (3) the RPE cells had a problem in lysing and voiding an ingested phagocytic load.

In conditions (1) and (2) a normal pigment epithelium is implicit, and in condition (3) the problems in the RPE could be secondary to biochemical anomalies within the outer segments, rendering them indigestible.

That there was relatively normal RPE throughout the eye, and that there were areas where the overlying photoreceptor cells were normal, degenerate, or non-existent, strengthens our conclusions that in this case the primary problem was in the photoreceptor cells. This was supported by experiments on the phagocytic behaviour of RPE cells from this patient grown in tissue culture.[17] In these, human

RPE cells were challenged with rod outer segments from cattle, and the number of particles engulfed per cell in cultures of our case 2 were statistically indistinguishable from the numbers engulfed by cells derived from normal human eyes. If this dynamic analysis of the phagocytic activity of these cells is a true representation of their in vivo capacity, then the extracellular accumulation of photoreceptor cell membranes in the mid peripheral retina must be an indication that these membranes are in some way undesirable or deficient in their ability to initiate phagocytosis.

Because of the complexity of the interactions between the photoreceptor cells and the RPE there is great potential for defects in a number of processes and at different cellular locations in giving rise to photoreceptor cell decay.[44] While we cannot identify the exact site or biochemical defect underlying the degenerative changes in either of our cases, we believe that these two patients are examples of inherited retinal dystrophies in which the defective gene expression occurs in different cell populations.

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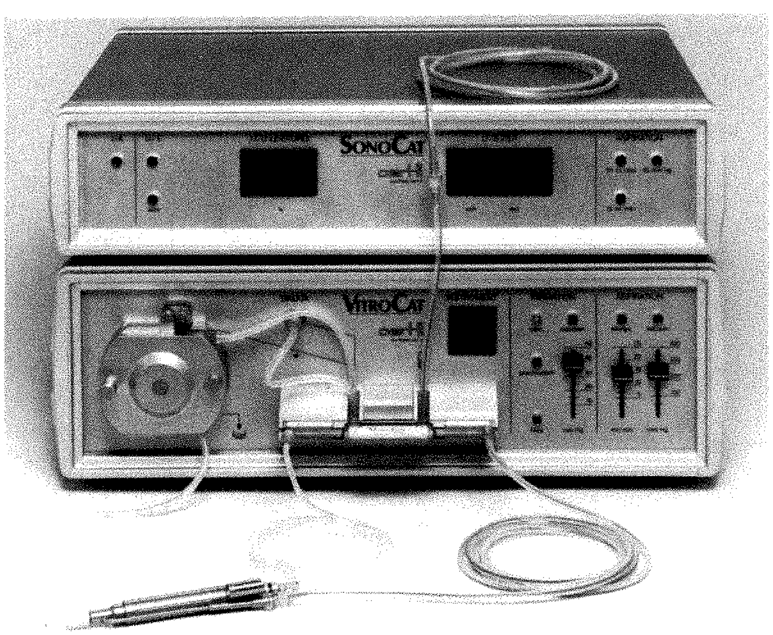

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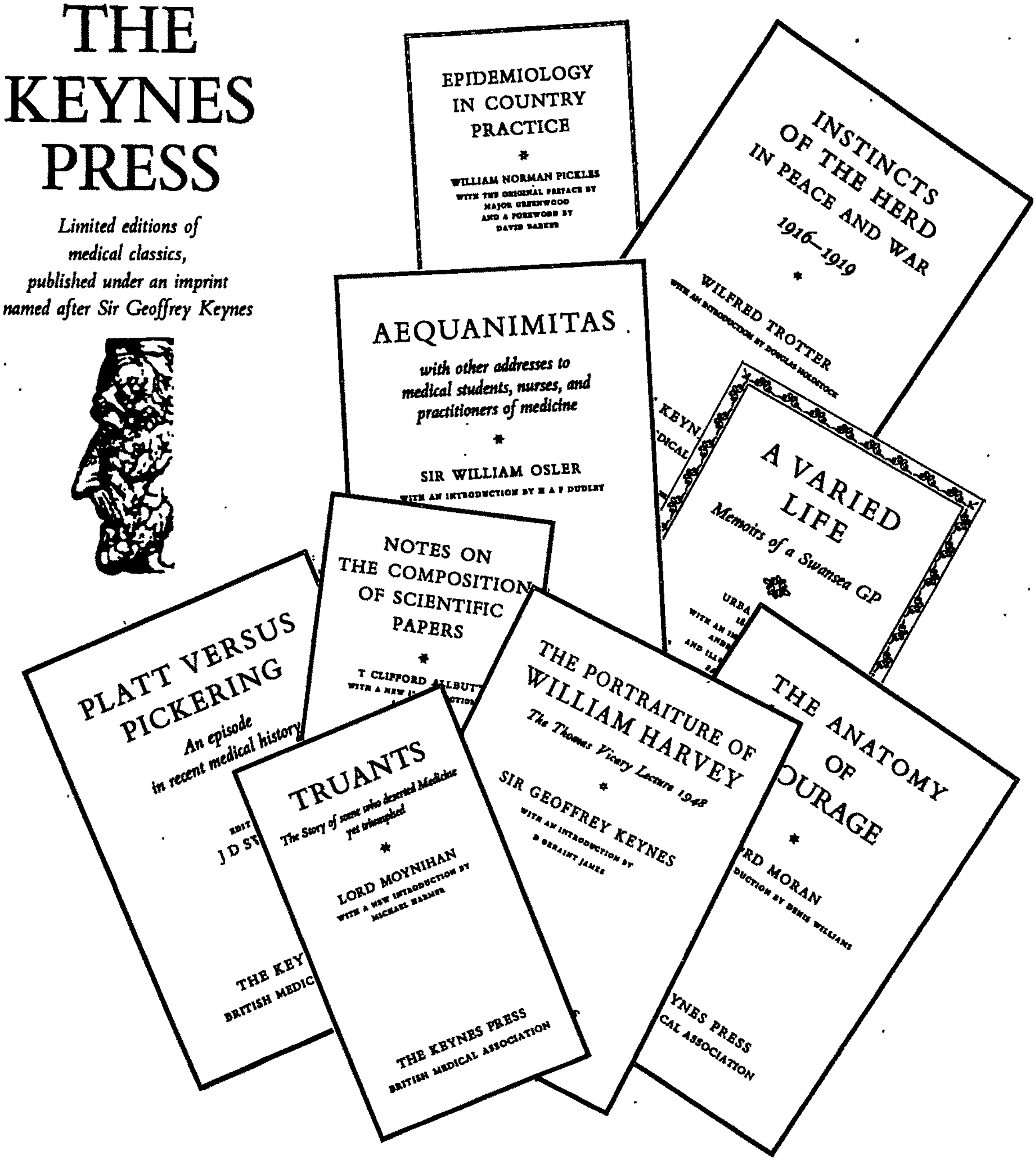
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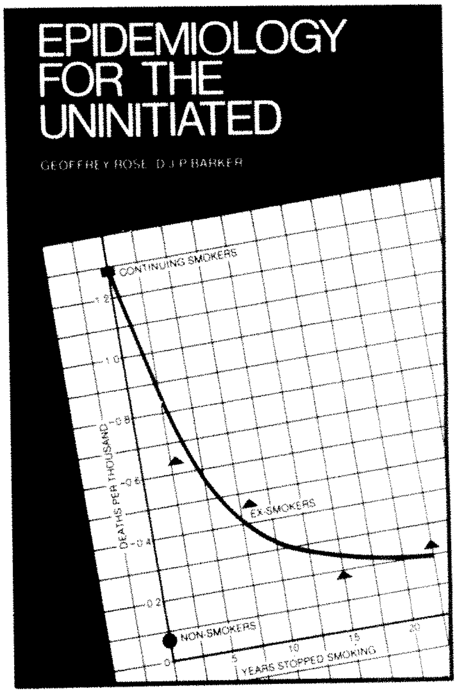

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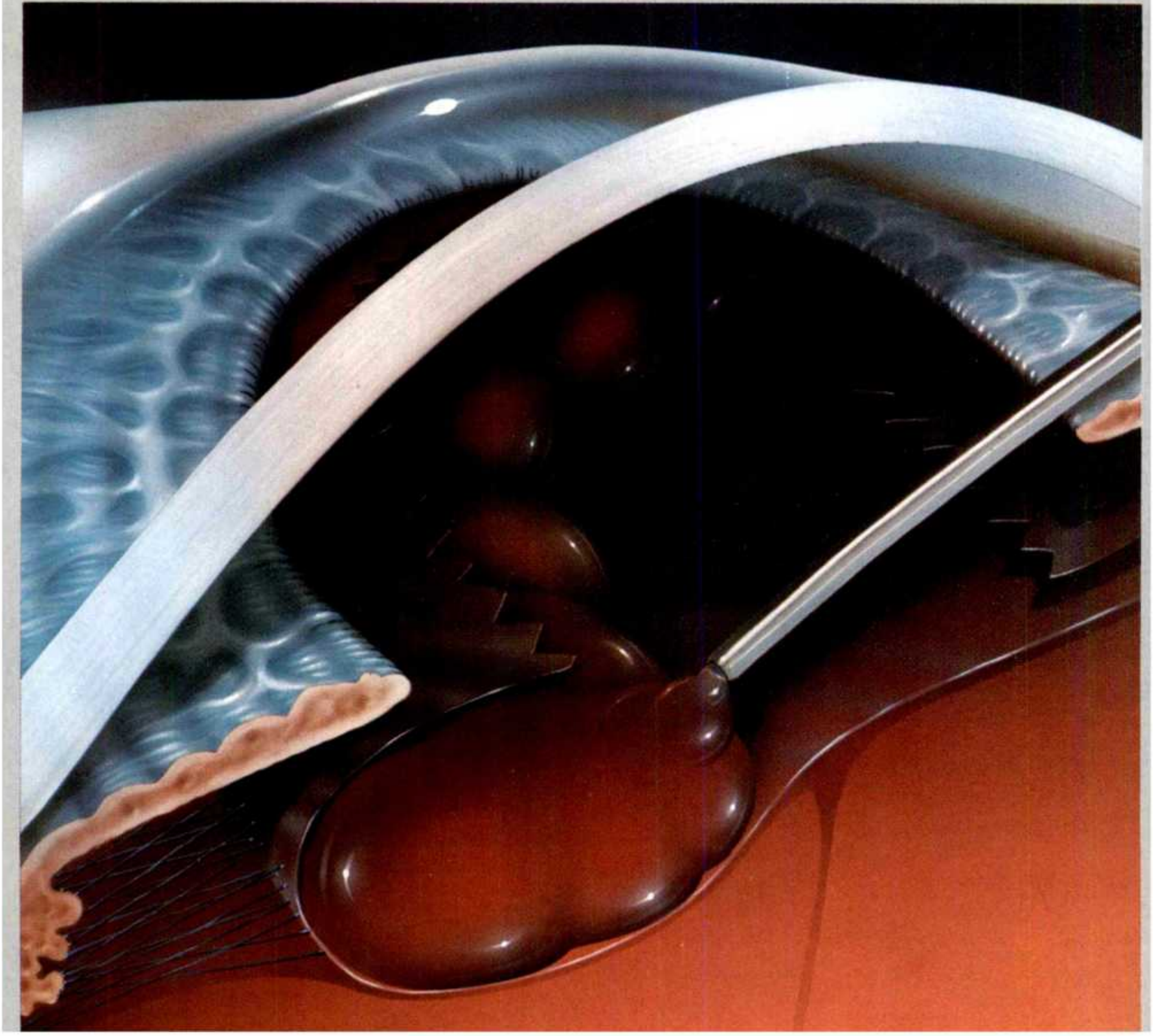

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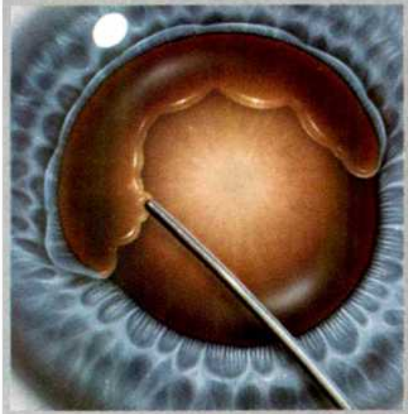

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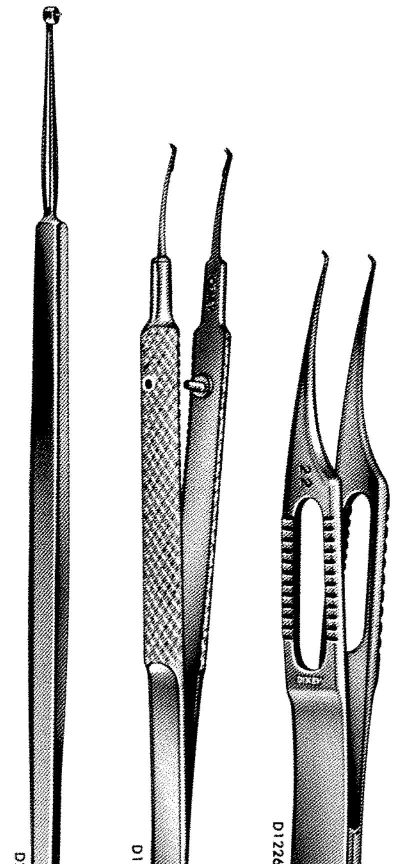

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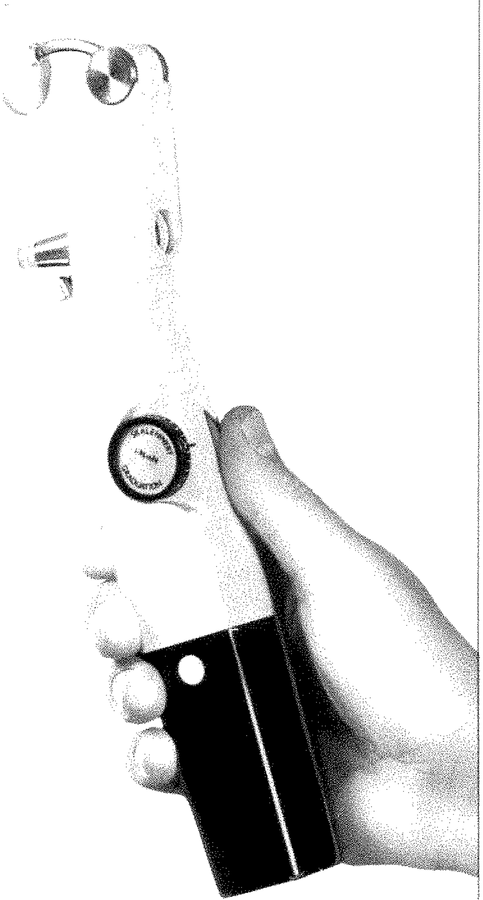

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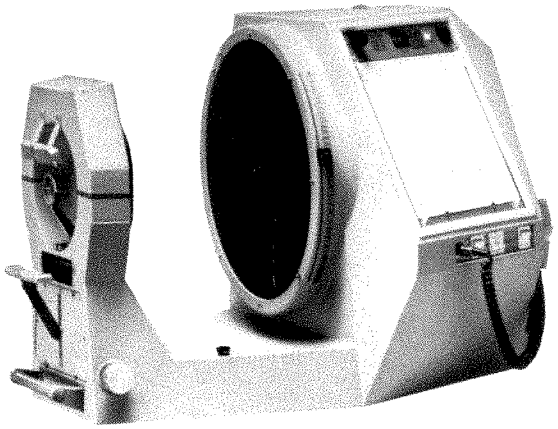

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Ophthalmic survey of a diabetic clinic.
I: Ocular findings

R H B GREY, N MALCOLM, D O'REILLY, AND A MORRIS

From the Bristol Eye Hospital, Bristol

SUMMARY A medical diabetic clinic was examined for evidence of diabetic eye disease. Of 681 patients invited for ocular examination 96·6% attended for screening. The results for insulin dependent diabetics (IDDs) and non-insulin dependent diabetics (NIDDs) were analysed separately and the major findings were: (1) Cataracts were present in 40·8% of IDDs and 46·2% of NIDDs, with an increased incidence with advancing age. For younger age groups there were significantly more cataracts in IDDs than in NIDDs ($p<0·001$). (2) Cataract extraction was required in 4·2% of the patients, which is higher than the general population. (3) The presence of retinopathy was related to the duration of diabetes ($p<0·001$) but not to age of onset of diabetes. (4) Retinopathy was found in 43·4% of IDDs and 20·1% of NIDDs. Sight threatening retinopathy was present in 13·3% of IDD and 4·3% of NIDD eyes. (5) Advanced diabetic eye disease was seen in 0·6% of eyes.

Diabetes mellitus has been shown to affect nearly all tissues of the eye.[1 2] Although some effects are mild or temporary with little visual threat, significant loss of vision can occur when patients develop cataracts or diabetic retinopathy.

Within the past decade improvements in therapeutic management of diabetic patients has led to a better visual prognosis,[3-17] though treatment can be time consuming for both patients and ophthalmologists.[18]

In order to plan treatment services for diabetic patients it is necessary to know the potential work load, which has been estimated as high, possibly to an extent that present services would be unable to cope. A study of patients attending a district general hospital diabetic clinic was undertaken in an attempt to assess the likely work load with which ophthalmologists may be faced. This report is concerned with the ocular findings which were noted during the assessment, and in view of the numbers of patients involved an opportunity was provided to compare insulin dependent diabetics (IDDs) with non-insulin dependent diabetics (NIDDs). Patients were included in IDD or NIDD groups according to their current diabetic treatment rather than on strict insulin dependency.

Patients and methods

A combined medical and ophthalmic clinic was organised for the purpose of this survey, and all patients attending the diabetic clinic at Weston General Hospital during 1981 were invited to attend. The diabetic clinic serves a circumscribed population, pursues a no-discharge policy, and reviews all patients at least once annually.

The patients attending had their corrected visual acuities recorded, slit-lamp examination of the anterior segment and vitreous, and their fundi examined after dilatation of the pupils. All fundus examinations were carried out by one observer (RHBG) using direct and indirect ophthalmoscopy and also contact lens examination in patients with more than minimal retinopathy. Details of the patients' medical and ophthalmic status were recorded on a proforma in order to enable easy transference of data, which were later analysed on the University of Bristol Computer Network.

To facilitate analysis the following criteria were used in the collection of the ophthalmic data:

Cataracts. Grade 0—no significant opacity; grade 1—opacity on slit-lamp but clear view of retina with direct ophthalmoscope; grade 2—retinal details partially obscured with direct ophthalmoscope but assessable with indirect ophthalmoscope; grade 3—

Correspondence to Mr R H B Grey, FRCS, Bristol Eye Hospital, Lower Maudlin Street, Bristol BS1 2LX.

details not accurately assessable with indirect ophthalmoscope; grade 4—aphakia.

Rubeosis iridis. Grade 0—absent; grade 1—peripupillary; grade 2—over iris surface.

Retinopathy. Background retinopathy was present if there were microaneurysms, dot haemorrhages, lipid exudates, cotton-wool spots, or microvascular abnormalities consistent with diabetes. Maculopathy was defined as macular oedema, hard exudates threatening the fovea, or foveal ischaemia at the time of the examination, regardless of previous laser treatment. Proliferative retinopathy was diagnosed if there was active vasoproliferation or the presence of fibrovascular tissue but was considered absent if previous treatment had led to complete regression of new vessels. In those patients in whom there was doubt whether there was either maculopathy or early neovascularisation present more detailed assessment, including fluorescein angiography, was performed on a subsequent occasion.

Advanced diabetic eye disease was diagnosed if thrombotic glaucoma, gross retinal ischaemia, traction retinal detachment, or phthisis bulbi was present.

Table 1 *Age of onset of diabetes*

Age (years)	*Male*	*Female*	*Both*	*% of total*
<10 years	4	6	10	1·5
10–19	18	15	33	5·0
20–29	17	8	25	3·8
30–39	28	12	40	6·1
40–49	49	37	86	13·1
50–59	86	63	149	22·7
60–69	109	88	197	29·9
70–79	41	63	104	15·8
80 or over	4	10	14	2·1
Total	356	302	658	100·0

Table 2 *Age at time of examination for IDDs and NIDDs*

Age (years)	*IDD (%)*	*NIDD (%)*
<40	46 (22·1)	4 (0·8)
40–49	28 (13·5)	31 (6·9)
50–59	32 (15·4)	68 (15·2)
60–69	49 (23·6)	144 (32·0)
70–79	48 (23·0)	162 (36·0)
80+	5 (2·4)	41 (9·1)
Total	208 (100)	450 (100)

Results

Six hundred and eighty-one patients were asked to attend the combined clinic, of which 658 were examined (96·6%). Twenty-three patients refused to attend on at least two occasions.

The sex incidence, age of onset of diabetes and type of diabetic treatment are outlined in Tables 1 and 2. There were 356 males and 302 females. 11% of males and 10% of females developed diabetes before the age of 30, and 13% of males and 24% of females were diagnosed after the age of 70 years; in nearly all age groups males outnumbered females. There was a marked difference in the age distribution of IDDs and NIDDs, with the latter being on average much older.

CATARACT

Slit-lamp examination showed some degree of lens opacity in 538 eyes of 289 patients, and in 103 eyes the opacities were considered to be severe enough to have some influence on vision—that is, grades 2 or 3. Dense cataract, considered to be a potential cause of marked visual loss, was present in only 16 eyes but 48 eyes were already aphakic at the time of examination. In five patients it was recommended that cataract extraction should be undertaken, bilaterally in two cases. At some time, therefore, cataract surgery was considered necessary in a total of 55 eyes (4·2% of the total). In three eyes extraction was recommended in order to facilitate laser photocoagulation for retinopathy, which would otherwise have been difficult to perform adequately. Extraction was contraindicated in 12 eyes with severe retinopathy because postoperative improvement in vision was considered unlikely.

Overall, the prevalence of cataract increased with the age of the patients (Table 3). When IDDs and NIDDs were analysed separately, it was found that 40·8% of IDD eyes and 46·2% of NIDD eyes had some degree of cataract. Although these figures were not significantly different, breakdown into age groups showed insulin dependency was associated

Table 3 *Numbers of eyes showing cataracts for IDDs and NIDDs by age at examination*

Age (years)	*IDDs*		*NIDDs*		χ^2	*p*
	No cataract (%)	*Cataract (%)*	*No cataract (%)*	*Cataract (%)*		
<50	124 (83·8)	24 (16·2)	70 (100)	0 (0·0)	11·154	<0·001
50–59	37 (57·9)	27 (42·1)	114 (83·8)	22 (16·2)	14·543	<0·001
60–69	62 (63·3)	36 (36·7)	185 (64·5)	102 (35·5)	0·008	NS
70+	23 (21·7)	83 (78·3)	114 (28·1)	292 (71·9)	1·436	NS
Total	246 (59·2)	170 (40·8)	483 (53·8)	416 (46·2)	3·152	NS

Table 4 *Severity of cataracts for IDDs and NIDDs by age at examination*

Age (years)	*IDDs*		*NIDDs*		χ^2	*p*
	Grade 0–2 (%)	*Grade 3&4 (%)*	*Grade 0–2 (%)*	*Grade 3&4 (%)*		
<50	144 (97·3)	4 (2·7)	70 (100)	0 (0·0)	0·719	NS
50–59	61 (95·3)	3 (4·7)	134 (98·5)	2 (1·5	0·764	NS
60–69	88 (89·8)	10 (10·2)	276 (96·2)	11 (3·8)	4·581	<0·05
70+	98 (92·5)	8 (7·5)	380 (93·6)	26 (6·4)	0·041	NS
Total	391 (94·0)	25 (6·0)	860 (95·5)	39 (4·5)	1·374	NS

Table 5 *Prevalence of cataract in men and women for IDDs and NIDDs*

Age (years)		*IDDs*				*NIDDs*			
		No cataract	*Cataract*	χ^2	*p*	*No cataract*	*Cataract*	χ^2	*p*
<50	Male	76	10	2·426	NS	48	0	—	—
	Female	48	14			22	0		
50–59	Male	25	17	0·014	NS	82	8	8·893	<0·001
	Female	12	10			32	14		
60–69	Male	24	16	0·118	NS	125	46	12·86	<0·001
	Female	38	20			60	56		
70–79	Male	6	36	1·789	NS	69	89	15·855	<0·001
	Female	15	39			37	129		
80+	Male	0	2	—	—	5	27	1·1	NS
	Female	2	6			3	47		
Total	Male	131	81	1·05	NS	329	170	66·1	<0·001
	Female	115	89			154	246		

Table 6 *Prevalence of cataract for IDDs and NIDDs with and without retinopathy*

	No retinopathy		*Retinopathy*		χ^2	*p*	*Not known*
	Cataract (%)	*No cataract (%)*	*Cataract (%)*	*No cataract (%)*			
IDD	73 (31·3)	160 (68·7)	93 (52·0)	86 (48·0)	17·05	<0·001	4
NIDD	314 (44·2)	397 (55·8)	93 (52·0)	86 (48·0)	3·192	NS	9
Total	387 (41·0)	557 (59·0)	186 (52·0)	172 (48·0)			13

Four IDD and nine NIDD eyes: retinopathy could not be assessed. All 13 eyes had cataract.

with a higher rate of cataract development for patients less than 60 years of age ($p<0·001$) but not in patients of 60 years or more.

Dense cataract was not found to be significantly different for IDDs and NIDDs at any age with the exception of the 60–69 year age group, in which a higher proportion of IDDs had dense opacities ($p<0·05$) (Table 4).

Cataract was found to be more common in females than males for the NIDD patients, and this difference was present in each age group (Table 5). There was no significant difference in the prevalence or severity of cataract for males and females among IDD patients nor severity of cataract in NIDDs.

Eyes with retinopathy showed a higher incidence of cataracts for IDD patients ($p<0·01$), but no significant difference was found for NIDD patients (Table 6). Proliferative retinopathy was not associated with a significantly higher rate of cataract than in eyes with non-proliferative retinopathy.

VITREOUS DETACHMENT AND HAEMORRHAGE

Identifiable detachment of the posterior hyaloid was seen in 437 eyes (33·2%), but examination for detachment of the posterior hyaloid was not possible in 45 eyes on account of media opacities, advanced diabetic eye disease, or previous vitrectomy (Table 7). The great majority of involved eyes showed the typical vitreous configuration of senile separation. For both IDD and NIDD patients there was an increase in the percentage showing posterior vitreous separation with age (17% for those less than 50 years old rising to about 40% for those of 70 years and over).

In eyes with retinopathy a highly significant increase in vitreous detachment was found for IDDs

Table 7 *Prevalence of vitreous detachment in IDDs and NIDDs by age at examination*

Age (years)	*IDDs*		*NIDDs*		χ^2	*p*	*Not known*
	No PVD (%)	*PVD (%)*	*No PVD (%)*	*PVD (%)*			
<50	117 (82·4)	25 (17·6)	58 (82·9)	12 (17·1)	0·0	NS	6
<50–59	45 (72·6)	17 (27·4)	108 (81·8)	24 (18·2)	1·641	NS	6
60–69	49 (52·1)	45 (47·8)	183 (64·9)	99 (35·1)	4·337	<0·05	10
70+	63 (61·2)	40 (38·8)	211 (54·7)	175 (45·3)	1·114	NS	23
Total	274 (68·3)	127 (31·7)	560 (64·4)	310 (35·6)	1·738	NS	45

PVD=Posterior vitreous detachment.

Table 8 *Vitreous detachment in eyes with and without retinopathy for IDDs and NIDDs*

	IDDs		*NIDDs*	
	No retinopathy	*Retinopathy*	*No retinopathy*	*Retinopathy*
No PVD	177 (77·6)	97 (56·1)	450 (64·3)	110 (65·1)
PVD	51 (22·4)	76 (43·9)	250 (35·7)	59 (34·9)
Total	228 (100·0)	173 (100·0)	700 (100·0)	169 (100·0)
χ^2	20·15		0·011	
p	<0·001		NS	
Not classifiable	15		30	

PVD=Posterior vitreous detachment.

Table 9 *Eyes showing retinopathy in IDDs and NIDDs by duration of diabetes*

Years diabetic	*IDDs*		*NIDDs*	
	No retinopathy (%)	*Retinopathy (%)*	*No retinopathy (%)*	*Retinopathy (%)*
<2	22 (84·6)	4 (15·4)	162 (92·0)	14 (8·0)
2–	58 (81·7)	13 (18·3)	229 (85·8)	38 (14·2)
5–	78 (81·2)	18 (18·8)	207 (78·1)	58 (21·9)
10–	28 (48·3)	30 (51·7)	76 (63·9)	43 (36·1)
15–	23 (41·1)	33 (58·9)	21 (52·5)	19 (47·5)
20+	24 (22·9)	81 (77·1)	16 (69·6)	7 (30·4)
Total	233 (56·6)	179 (43·4)	711 (79·9)	179 (20·1)

In four IDD and nine NIDD eyes the presence of retinopathy could not be determined.

(p<0·001). This was not true for NIDDs (Table 8). Eyes with proliferative retinopathy showed vitreous detachment in all but two cases, in which there were flat new vessels arising in the retinal periphery.

Vitreous haemorrhage was present in 12 eyes (0·9%). Six IDDs had vitreous haemorrhage, of which five had had diabetes for over 20 years and one case bled between two and five years. Vitreous haemorrhage tended to occur earlier in NIDDs, with one before two years after the diagnosis of diabetes, two between two and five years, one between five and 10 years, and one between 15 and 20 years. Vitrectomy was recommended in six eyes, but in the remaining six eyes surgery was not recommended as it was considered that either the blood would clear spontaneously or that the diabetic retinopathy was too advanced for visual improvement.

In 15 eyes (1·1%) cataract or advanced diabetic eye disease prevented assessment of the presence of vitreous haemorrhage.

RETINOPATHY

Retinopathy was present in 358 eyes (27·2%) of 200 patients (30·3%). The prevalence of retinopathy in IDDs and NIDDs related to the duration of the diabetes is shown in Table 9. For both IDDs and NIDDs the proportion of patients with retinopathy tended to increase with duration of diabetes and this trend was highly significant (p<0·001). Only 23 NIDDs had diabetes for 20 years or more (Fig. 1). However, age of onset was found to be of less significance than duration of diabetes with regard to the prevalence of retinopathy (Table 10).

There was no difference in the prevalence of retinopathy for males or females in either IDDs or NIDDs in any age group. In 13 eyes the presence of

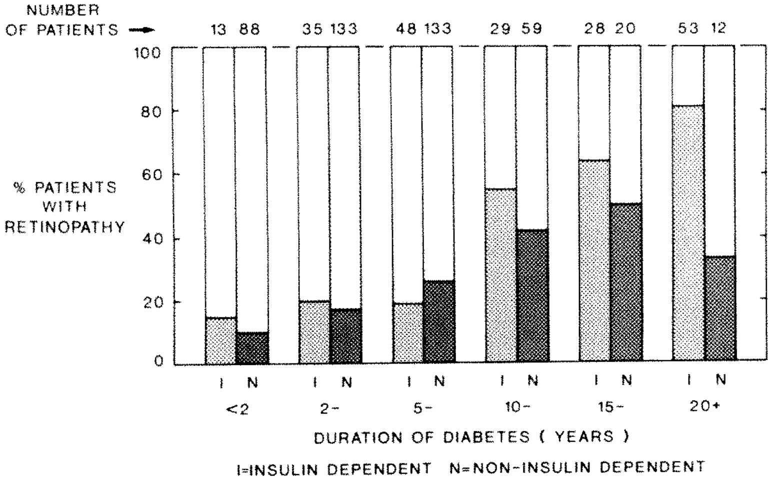

Fig. 1 *Histogram showing percentage of patients with retinopathy related to duration of diabetes.*

retinopathy could not be determined because of opacities in the media.

In 358 eyes with retinopathy, only background changes were present in 267 (20·3% of all eyes and 74·6% of retinopathic eyes). The serious forms of retinopathy, namely maculopathy and proliferative retinopathy, are listed in Table 11. The prevalence of both background and serious retinopathy was higher in IDD than NIDD patients. In IDDs 127 eyes (30·8%) had background and 47 eyes (11·3%) had serious retinopathy, whereas in NIDDs 140 eyes (15·7%) had background and 38 (4·3%) serious retinopathy. If only those eyes with microangiopathy were considered, the difference in prevalence of serious retinopathy between IDDs and NIDDs was much less—26·3% of IDDs and 21·2% of NIDDs.

In 38 patients (5·8%) retinopathy was present in only one eye. In one case the retinopathy had progressed to maculopathy, but in all the remaining 37 cases background changes only were present. No patients in the study had proliferative retinopathy or advanced diabetic eye disease in one eye without some microvascular changes in the fellow eye.

One hundred and fifty-eight patients had retinopathy in both eyes. Of these 103 had background changes only bilaterally. Twenty-two patients had background retinopathy in one eye with serious retinopathy in the fellow eye (15 with maculopathy, six with vasoproliferation, and one advanced diabetic eye disease). Thirty patients had bilateral serious retinopathy and two had serious retinopathy in one eye with advanced disease in the other. One patient had advanced eye disease in both eyes.

Table 10 *Prevalence of retinopathy by age of onset of diabetes*

Duration of diabetes (years)	*Age of onset of diabetes (years)*	*IDDs*		*NIDDs*	
		No retinopathy	*Retinopathy (%)*	*No retinopathy*	*Retinopathy (%)*
<10	<40	52	2 (3·7)	10	4 (28·6)
	40–59	53	15 (22·1)	194	36 (15·7)
	60+	53	18 (25·4)	394	70 (15·1)
10+	<40	38	87 (69·6)	13	7 (35·0)
	40–59	25	51 (67·1)	59	35 (37·2)
	60+	12	6 (33·3)	41	27 (39·7)

Table 11 *Severity of retinopathy (with percentages) for IDD and NIDD eyes*

	Nil (%)	*Background only (%)*	*Maculopathy (%)*	*Proliferative (%)*	*Advanced (%)*
IDD	233 (56·6)	127 (30·8)	32 (7·8)	24 (5·8)	9 (2·2)
NIDD	711 (79·9)	140 (15·7)	31 (3·5)	9 (1·0)	1 (0·1)
Total	944 (72·5)	267 (20·5)	63 (4·8)	33 (2·5)	10 (0·8)

In four IDD and nine NIDD eyes the presence of retinopathy could not be determined.

RUBEOSIS IRIDIS AND ADVANCED DIABETIC EYE DISEASE

Rubeosis iridis was not a common finding. Ten eyes were seen with fine vessels around the pupil margin, and three eyes had rubeosis extending over the whole iris surface. Gonioscopy was not undertaken to examine the drainage angle for signs of peripheral new vessels.

Advanced diabetic eye disease was seen in less than 1% of eyes. Two eyes showed gross retinal ischaemia without signs of proliferative retinopathy, five eyes had traction retinal detachments, one eye had thrombotic glaucoma, and two eyes had become phthisical.

CONCOMITANT EYE DISEASE

One hundred and sixty-eight eyes of 122 patients showed ocular disorders other than diabetes which were considered serious enough to have affected vision to some degree (Table 12). No relative quantitative assessment of visual loss was undertaken in these patients, but in many cases the concomitant disorder was of greater visual significance than the diabetic retinopathy. The prevalence of retinopathy in eyes with myopia and chronic simple glaucoma was lower than the prevalence in the remainder of the series.

Discussion

CATARACT

The prevalence of cataract in the diabetic population has been reported as varying from 6% to 45%, with increasing age showing a marked effect on the figures.[1,19,20]

Caird[20] has excellently reviewed the subject of epidemiology of cataracts in diabetes. The absence of non-diabetic patients in this study precludes firm inferences on the role of diabetes in the development of cataract. The figures concur with previous reports of a lower incidence in younger than older patients—that is, 9% in those under 40 years rising to 89% in those over 80 years—but whether diabetes is a major influence on this increase with age has been questioned.[20,21] The current study showed that the prevalence of cataract in IDDs was significantly higher than in NIDDs less than 60 years of age but not in the older age groups.

Table 12 *Eyes with concomitant ocular disease*

	Number	*No. with retinopathy*	*%*
Senile macular atrophy	43	11	25·6
Myopia	33	5	15·2
Chronic simple glaucoma	23	2	8·7
Ambolyopia	18	4	22·2
Disciform macular degeneration	10	1	10·0
Corneal scarring	10	3	30·0
Preretinal traction membrane	7	4	57·1
Ischaemic optic neuropathy	5	1	20·0
Uveitis	5	0	—
Branch vein occlusion	3	0	—
Central vein occlusion	3	0	—
Miscellaneous	8	1	12·5

Cataract extraction was recommended for seven eyes and had already been undertaken previously in 48 eyes. This resulting high extraction rate of 4·2% is in agreement with previous reports in diabetic patients[22] and is higher than might be expected in the general population.[23]

The presence of known diabetic involvement of the eye (i.e., retinopathy) appeared to have some association with the presence of cataracts in IDDs; 52·6% of patients with retinopathy had cataracts compared with 38·2% of patients without retinopathy ($p<0·01$). The difference was much smaller in NIDDs, 22·4% and 18·5% respectively, and was not statistically significant. This finding together with the high prevalence rate of both cataract and retinopathy in IDDs might suggest some common pathogenetic factors for both these diabetic complications.

RETINOPATHY

It has been established that retinopathy, potentially the most serious of the ocular complications of diabetes and one of the most debilitating generally, becomes more prevalent as the duration of the disease increases.[1,24–31]

This study concurs with these findings. Previous reports have tended to consider IDDs alone or all types of diabetes together and suggested that the prevalence of retinopathy rose from about 15% at five years to 60% at 15 years and 75% at 20 years.

Donovan, in a prospective study,[32] showed an overall incidence of retinopathy in his diabetic patients of 22·7%, which was slightly lower than the 30·3% of the present study. He used direct ophthalmoscopy only, and this may account for the slightly lower figure.[29] Unfortunately his work could not be completed and the precise ophthalmic details were not published. It was thought that 6·1% of patients had maculopathy (4·9% of eyes in the present study) and 4·4% had proliferative changes (2·5% in the present study). Only one-third of Donovan's patients with retinopathy had previously attended an ophthalmologist; thus his slightly higher figures for the more severe forms of retinopathy may be a result of fewer referrals for photocoagulation.

Scobie *et al.*[18] reviewed 1000 consecutive diabetic patients attending a diabetic clinic. They found 26·7% had retinopathy and 9·5% had serious retinopathy—that is, maculopathy, proliferative changes, or signs of retinal ischaemia. The latter group was not categorised in this survey, but Scobie found roughly equal numbers of maculopathy and proliferative patients. This contrasts with the present findings of maculopathy being twice as common as neovascularisation, though there was no gross difference in the age structure or diabetic treatment of the patients in the two studies.

Analysis of the treatment groups separately showed that proliferative retinopathy was almost six times more common and maculopathy was twice as common in IDDs as in NIDDs. Although this association in proliferative retinopathy is well recognised, the latter finding was not expected.[33] The much larger number of patients not requiring insulin has led presumably to the impression of maculopathy being more common by weight of numbers.

Advanced diabetic eye disease was found in only 0·6% of eyes. This low figure may be a reflection of the efficacy of photocoagulation, which had been already carried out on a number of the patients.[34] However, 23 patients failed to attend for examination, and it is likely that some of these cases did so because they already had severe ocular complications of diabetes.

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Ophthalmic survey of a diabetic clinic: II. Requirements for treatment of retinopathy

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SUMMARY The eyes of 658 patients attending a district general hospital diabetic clinic were examined for retinopathy requiring treatment by photocoagulation or vitreoretinal surgery. Although the majority of patients with serious retinopathy were already under ophthalmic supervision, 39 cases (52 eyes) were found which required treatment. Eighty eyes had had previous photocoagulation, and treatment was recommended for maculopathy in 40 eyes, proliferative retinopathy in seven eyes, and combined maculopathy and proliferative retinopathy in five eyes. This suggested that existing referral criteria for photocoagulation in the population studied were reasonably accurate for proliferative retinopathy, but maculopathy was more frequently overlooked. In insulin dependent patients (IDDs) undetected maculopathy was found in 17/416 eyes, (4·0%) and in non-insulin dependent patients (NIDDs) 28/899 (3·1%). Untreated proliferative retinopathy was discovered in 5/416 (1·2%) IDD eyes and 7/899 (0·8%) of NIDD eyes. Vitreoretinal surgery was required in six eyes (0·5%) for vitreous haemorrhage or traction retinal detachment. Equipment for the treatment of diabetic retinopathy is now almost universally available in ophthalmic departments, but time for patient management by trained staff may be inadequate. Each UK ophthalmic consultant needs approximately 100 sessions per year to monitor and treat known cases of retinopathy apart from time required to train junior staff.

The treatment of diabetic retinopathy requires the major part of the time to be devoted to retinal photocoagulation by ophthalmologists. The necessity of photocoagulation in the treatment of diabetic maculopathy[1-4] and proliferative retinopathy[5-11] has been conclusively shown. In addition, for those cases with persistent vitreous haemorrhage or traction retinal detachment, vitrectomy and segmentation of diabetic fibrovascular tissue has been shown to improve vision in a large proportion of patients.[13-17]

In order to plan services for effective patient management it is necessary to know the likely work load involved in terms of photocoagulation and vitreous surgery. A study was therefore devised to examine diabetic patients in a general hospital in an attempt to define the probable resources required for management of diabetic patients.

Patients and methods

The patients studied and the methods employed have been previously described.[18] In brief, the entire diabetic clinic of the General Hospital at Weston-super-Mare was examined prospectively in a purposely formed combined medical and ophthalmic clinic. The diabetic and ocular details were recorded on a proforma designed for later computer analysis. Among the data recorded were the presence and severity of retinopathy, the type of diabetic treatment the patients were receiving, previous photocoagulation treatment and whether the patients were under regular ophthalmic review (defined as examination by an ophthalmologist within the previous two years).

Diabetic maculopathy was considered treatable and recommended for laser photocoagulation if there was foveal oedema or exudates were encroaching on the fovea. Proliferative retinopathy was recommended for treatment if vasoproliferation was active, but not if previous photocoagulation had induced regression or quiescence of the proliferative process.

In order to facilitate analysis patients were assigned to one of four groups depending on insulin or non-insulin dependency (IDD or NIDD) and whether they were under ophthalmic supervision by

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an ophthalmologist: *group A*, IDD and seen by an ophthalmologist within two years; *group B*, IDD and not seen by an ophthalmologist for at least two years; *group C*, NIDD and seen by an ophthalmologist within two years; *group D*, NIDD and not seen by an ophthalmologist for at least two years.

Results

Six hundred and eighty-one patients were asked to attend the combined clinic, of which 658 (96·6%) were examined. Two hundred and eight patients (31·6%) were insulin dependent diabetics (IDDs) and 450 (68·4%) were non-insulin dependent diabetics (NIDDs).

RETINOPATHY AND PHOTOCOAGULATION

The previous attendance and photocoagulation records are shown in Tables 1 and 2.

Insulin dependent patients

Group A consisted of 86 patients whose eyes had been examined within the previous two years (41·3% of IDDs). One hundred and nine eyes (64·5%) of this group had retinopathy, of which 51 eyes had undergone previous photocoagulation. Twelve eyes (7·1%) required photocoagulation for maculopathy and three eyes (1·3%) for proliferative retinopathy. Eleven eyes had quiescent proliferative retinopathy following previous photocoagulation.

Group B contained 122 patients whose eyes had not been examined within the past two years (58·7% of IDDs). In this group 70 eyes (28·8%) showed retinopathy, of which five required treatment for maculopathy (2·1%) and two for proliferative retinopathy (0·8%). In four IDDs the presence of retinopathy could not be determined on account of opacities in the media.

Non-insulin dependent patients

Group C had 109 patients (24·2% of NIDDs). Of the 211 eyes examined in this group 73 (34·6%) showed retinopathy, and previous photocoagulation had been carried out on 29. Laser photocoagulation was recommended for 14 eyes (6·6%) for maculopathy and for five eyes (2·4%) with proliferative retinopathy. One eye had persistent, quiet fibrovascular tissue following laser treatment, which did not require further photocoagulation.

Group D consisted of 41 patients (75·8% of NIDDs). One hundred and six eyes in this group had retinopathy (15·6%). Fourteen eyes (2·1%) were recommended for treatement for maculopathy and two eyes (0·2%) for proliferative retinopathy. The presence of retinopathy in nine NIDD eyes could not be determined.

Tables 3 and 4 show the numbers of eyes with

Table 1 *Patient groups and numbers of eyes*

	IDD	%	*NIDD*	%
Eyes examined within two years	Group A: 169	40·6	Group C: 211	23·5
Eyes not examined within two years	Group B: 243	58·5	Group D: 679	75·5
Not assessed	4	0·9	9	1·0
Total	416	100	899	100

IDD=Insulin dependent. NIDD=Non-insulin dependent.

Table 2 *Eyes showing retinopathy*

	Group A	*%*	*Group B*	*%*	*Group C*	*%*	*Group D*	*%*
No retinopathy	60	35·5	173	71·2	138	65·5	573	84·4
Retinopathy	109	64·5	70	28·8	73	34·6	106	15·6
Total	169	100	243	100	211	100	659	100
Not assessed	3		1		7		2	

Table 3 *Eyes with serious retinopathy recommended for treatment*

Group	*No.*	*Maculopathy only*	*Proliferative retinopathy only*	*Maculopathy plus proferative retinopathy*	*Total*
A	172	10	1	2	13
B	244	5	2	–	7
C	218	11	2	3	16
D	681	14	2	–	16
Total	1315	40	7	5	52

Table 4 *Eyes with proliferative retinopathy*

Group	*NVD*		*NVE*		*NVD+NVE*		*Total*	
	Active	*Inactive*	*Active*	*Inactive*	*Active*	*Inactive*	*Active*	*Inactive*
A	1	11	2	3	–	5	3	19
B	–	–	1	–	1	–	2	–
C	2	1	2	1	1	–	5	2
D	–	–	2	–	–	–	2	–
Total	3	12	7	4	2	5	12	21

NVD=New vessels on disc. NVE=New vessels elsewhere.

serious retinopathy in all groups. There were 21 eyes in which previous photocoagulation had led to regression of active vasoproliferation and did not require further treatment although some fibrous tissue persisted. Sixty-three (48·0%) eyes were discovered to have maculopathy, and 45 were recommended for photocoagulation. The remaining 18 eyes were judged to be too advanced for treatment to be beneficial.

Twelve eyes (0·9%) were found to have active proliferative retinopathy, and all were recommended for photocoagulation. Of these 12 eyes three had disc new vessels, seven had peripheral new vessels, and two had both disc and peripheral new vessels.

Combined maculopathy and active proliferative retinopathy was seen in five eyes, all of which were recommended for laser photocoagulation. One eye was found to have a posterior retinal tear from vitreous traction, and this was treated by laser.

VITRECTOMY

Out of a total of 1315 eyes in the whole study six were recommended for vitreoretinal surgery (0·5%). All these patients had previously received photocoagulation, and all but one were IDD. There were five further patients with vitreous haemorrhage who were not recommended for surgery as it was thought either the haemorrhage would clear spontaneously or the underlying retinal ischaemia was too advanced for visual improvement to occur.

Six eyes (0·5%) had advanced diabetic eye disease and were beyond treatment.

Discussion

The management of diabetic retinopathy is a cause for concern both to physicians running diabetic clinics and to ophthalmologists.[19] Prior to the survey clinic described here referral for ocular examination in Weston-super-Mare was either by general practitioners or by physicians managing the diabetic clinic. When patients had visual symptoms, or if retinopathy was noted on ophthalmoscopy, an ophthalmic opinion was requested. The low prevalence of most forms of serious retinopathy in those patients who had not had their eyes previously examined by an ophthalmologist before suggests that this method of referral is moderately efficient, at least for proliferative retinopathy. However, maculopathy tended to be overlooked in 2%–3% of eyes in IDDs and NIDDs. In this study more than half the IDDs were not under ophthalmic supervision (group B), and, of these, 28% had retinopathy, of which 10% needed treatment. Although this might suggest this is an 'at risk' group, those already under supervision (groups A and C) had almost equal rates of treatable retinopathy. When group D was compared with group B, the prevalence of retinopathy was less, but, once it was present, the proportion requiring treatment was similar.

For ophthalmologists it would appear that the very time consuming exercise of screening large numbers of diabetics would not be justified, as relatively few additional patients would be identified for treatment of retinopathy. It would probably be more appropriate to ensure that the physicians responsible for the primary diabetic care could broadly assess retinopathy, and also for patients to have visual acuity measurements to reduce the number of missed maculopathy cases. Cases in which retinopathy is identified should probably be referred for ophthalmic opinion.

The catchment population of Weston General Hospital is approximately 92 000. The primary ophthalmic assessment of the diabetic cases attending the diabetic clinic is carried out within the same hospital. Not all diabetic patients in the district are referred to hospital by their general practitioners, and the numbers of diabetics seen in this survey (7·4 per 1000 population) are lower than the estimated UK prevalence of diabetics of about 10 per 1000.[20] Nevertheless the spectrum of retinopathy seen in this survey is probably similar to that found in other non-teaching district general hospitals. If the figures in this study are representative of the diabetic population as a whole, at least 8·0% of diabetic eyes will require laser photocoagulation at some time, of which approximately 80% will be for maculopathy and 20% for proliferative retinopathy. These figures are not greatly different for IDDs compared with NIDDs, although there is a slightly higher prevalence of proliferation and maculopathy in IDDs.[18]

The time needed for such photocoagulation treatment varies. Scobie *et al.*[21] suggested that maculopathy requires 30 minutes per treatment session and proliferative retinopathy up to two hours, the time depending on the number of sessions, the patient's tolerance, and the operator's skill. Using these times, with which we are in broad agreement, we found that this survey produced an additional treatment requirement of 44 hours above the treatment which has already been administered, in spite of two consultant opthalmologists with an interest in diabetic retinopathy managing the diabetic patients attending the hospital. In the UK there are 412 consultant ophthalmologists serving 56 million citizens, and at the rates found in this survey each consultant might be required to give nearly 65 hours additional laser photocoagulation to diabetics. No data were collected on the fresh incidence of treatable retinopathy, and therefore it is not possible to calculate the long-term requirements for supervision and treatment of new cases, but the time required for monitoring patients with known retinopathy can be assessed. On a conservative assumption that a single 20-minute examination a year is necessary for background retinopathy, and, say, six visits a year are required for patients needing photocoagulation, then the clinic population studied required 193 hours per year for outpatient attendances regardless of treatment time. On a national scale each consultant could require 285 hours or 82 sessions per year to examine diabetics and a possible further 18 sessions for photocoagulation. As pointed out by Blach,[19] the major limiting factor for the proper management of retinopathy is no longer equipment availability but lack of trained staff. The above calculations do not take account of time required to train junior staff in assessment or photocoagulation of diabetic retinopathy.

The number of diabetic eyes requiring vitrectomy is low (0·5%). However, calculating from a known 681 diabetic patients in a population of 92 000 suggests that 3876 eyes may need vitrectomy in a UK population of 56 million—that is, 9 or 10 eyes per consultant ophthalmologist. If two such operations were carried out per week, 20 specialist vitrectomists would take two years to complete the work regardless of other conditions or of new diabetic cases needing vitrectomy. Owing to the expense of equipping an operating theatre for vitrectomy work it would seem reasonable to set up specialist centres, but the present number of such centres in the UK is woefully inadequate. It is to be hoped that in the future the number of eyes requiring vitrectomy will be reduced gradually as improved management by photocoagulation reduces the prevalence of uncontrolled proliferative retinopathy.

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Effects of increasing numbers of phagocytic inclusions on human retinal pigment epithelial cells in culture: a model for aging

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SUMMARY Cultures of human retinal pigment epithelial cells have been challenged with a number of biological (lipofuscin, melanin, and rod outer segments) and non-biological (latex microspheres) particles at a variety of concentrations. The particles were chosen to include examples of both degradable and non-degradable systems. A range of morphological changes were observed by phase contrast microscopy, and these became more atypical with increasing concentration. At the highest concentration cells had ingested so many particles that many had died and others had ruptured. The time course of these changes indicated a relationship between cellular lytic activity and the capacity of the particle to degrade. The potential of this system as a model for studying senescence is discussed.

The retinal pigment epithelium (RPE) differentiates early in embryogenesis, and thereafter little if any cell division occurs in this layer[1] other than in response to acute injury, such as laser induced damage.[2] With increasing age some cells die and are lost from this layer. Those remaining migrate and increase in surface area to ensure the integrity of the epithelial sheet and maintain its blood-retinal barrier properties. This aging population of cells also has a unique role in phagocytosing the spent tips of rods and cones.[3,4] Thus, unlike any other macrophage which has a transient existence and having fulfilled its role by ingesting its target material then dies, the same pigment epithelium cells must continuously engulf photoreceptor elements on a diurnal basis for 70 years or more.

Once inside the pigment epithelium the outer segments undergo lysis, which results in their progressive degradation.[5-7] Some of the breakdown products of this process may be recycled back to the photoreceptor cells, while others are voided into the choriocapillaris via Bruch's membrane.

The lipofuscin granules seen within the pigment epithelial cells[8-10] have been attributed to the retention of incompletely degraded remnants of phagocytosed photoreceptor outer segments,[6,11] and as they represent the accumulation of a non-functioning molecule they must be an indication of cell senescence.[12] Since lipofuscin is not initially extruded from the cell but slowly accumulates with the passing years, it is particularly obvious in the tissues of older people, increasing from 8% of cell volume to 20% between the ages 40 and 80 years. This accumulation is particularly apparent in the RPE of the macula,[10] and has been stated by some authors as the reason why RPE cells from this location grow less actively in culture than those from peripheral sites,[13] the implication being that the higher the lipofuscin content the more 'senile' the cell.

Quantitative analysis of the accumulation of lipofuscin within the RPE is complicated by the presence of melanin granules, as the two may closely resemble each other. Melanin granules are also constantly exposed to lysosomal enzymes[14] but in general appear to be little affected by them[15] though melanolysosomes are sometimes identified.[16] In some instances melanin granules appear in complex inclusions together with lipofuscin; these are termed melanolipofuscin and assume a variety of forms dependent on the dominant component.[9]

Studies of RPE from various animal species have shown that, in addition to phagocytosing the terminal ends of outer segments, the RPE is also capable both in vitro and in vivo of ingesting latex microspheres, carbon particles, liposomes,[17-20] and, in the case of chick RPE, bacteria.[21]

When human RPE cells are isolated and grown in

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tissue culture the cells become progressively depigmented as a result of the dilution of both melanin and lipofuscin granules among a rapidly increasing number of daughter cells.[22,23] In such situations loss of melanin may decrease the cells' protective mechanisms by removal of both a light absorbing system[24] and a free radical scavenger.[25] However, loss of lipofuscin may effectively rejuvenate daughter cells by eradicating a product of senescence.[26]

Previous experiments have shown that depigmented cells will readily ingest both melanin and lipofuscin granules when these are presented in the culture medium and that they will retain the ingested pigment granules within their cell cytoplasm.[27] This study is an attempt to simulate cellular senescence by challenging cultures of RPE cells with increasing concentrations of a variety of degradable and non-degradable biological particles and non-degradable abiotic particles.

Methods and materials

CELL CULTURE

Post-mortem eyes from six persons with no known ophthalmic disease were obtained from various hospitals in London. Donor eyes ranged from a 16-week fetus to a 91-year-old adult. Eyes from two dystrophic donors were obtained via the British Retinitis Pigmentosa Society's eye donor scheme. One donor was a 4-year-old child with Laurence-Moon-Biedl syndrome and the other a 68-year-old sufferer from retinitis pigmentosa. All eyes were processed between 24 and 48 h following death.

Human RPE cells were isolated and cultured by the techniques previously described.[28,29] The need to increase the amount of tissue available from any given donor dictated that all cells had undergone four to seven passages.

Cultures for experiments were grown either in eight-chamber tissue culture slides or in 17 mm multiwells (Flow).

EYE CUP PREPARATION

Two eyes were received 24 h post mortem, one from a 7-year-old girl and the other from a 58-year-old man. Eye cups were prepared by a modification of the cylinder technique.[28] The eye cup, devoid of vitreous and neural retina, was dissected into five segments, four segments from the periphery and one from the macular region. Stainless steel cylinders were placed on selected areas of each segment before being filled with either medium alone or medium supplemented with lipofuscin.

Rod outer segment isolation. Bovine rod outer segments were isolated from fresh retinae by the technique of Papermaster.[30]

Melanin and lipofuscin isolation. Melanin and lipofuscin were isolated as previously described.[25]

CHALLENGE

Confluent cultures of human RPE cells grown on either eight-chamber slides or 17 mm multiwells were challenged with 0·3 ml or 1 ml respectively of growth medium containing one of the following:

(*a*) 0·8 μm diameter latex microspheres (Sigma), final concentration $3\cdot0\times10^{8}$, $3\cdot0\times10^{7}$, or $3\cdot0\times10^{6}$/ml;

(*b*) 0·5 μm–1·4 μm diameter lipofuscin granules at a final concentration of $3\cdot0\times10^{8}$, $3\cdot0\times10^{7}$, or $3\cdot0\times10^{6}$/ml;

(*c*) melanin granules at a final concentration of $3\cdot0\times10^{8}$, $3\cdot0\times10^{7}$, or $3\cdot0\times10^{6}$/ml (the dimensions of these fusiform granules were 1·0 μm in their short axis and 2·5 μm in their long axis);

(*d*) bovine rod outer segments at a final concentration of $3\cdot0\times10^{8}$, $3\cdot0\times10^{7}$, or $3\cdot0\times10^{6}$/ml (the dimensions of outer segment fragments ranged from 1·5 μm to 4·0 μm).

At appropriate time periods after challenge (see 'Results') the cells were examined by phase contrast bright field and electron microscopy.

Because of the difficulty in obtaining fresh human donor material both of the specimens obtained within 24 h post mortem were challenged with an identical medium in an attempt to reduce experimental error. They were both exposed to 0·25 ml of growth medium containing $3\cdot0\times10^{8}$ lipofuscin particles per ml and incubated at 37°C in a carbon dioxide incubator. Cells were processed 24 h after challenge for light microscopy.

MICROSCOPY

Inverted microscopy. The gross morphological appearance of cell cultures was observed on a number of occasions throughout the exposure period by an inverted microscope (Leitz Diavert). At selected times cultures were rinsed with Dulbecco's phosphate buffered saline (PBSA) and prepared for high resolution microscopy as follows:

Fluorescence microscopy. The cells were fixed for 1 h at room temperature with 3·5% paraformaldehyde in PBSA, washed with PBSA, and covered with coverslips wet mounted on glycerol/water (1:1). Slides were examined by a Zeiss fluorescent microscope (a BP-450-490 exciter and an LP 520 barrier filter).

Bright field light, and electron microscopy. The cells were fixed for 2 h at 4°C with 2% glutaraldehyde in 0·1 M cacodylate buffer, and postfixed for 1 h at 4°C in 1% osmium tetroxide in 0·1 M cacodylate buffer before being dehydrated in ethanol. Poly/Bed 812 (Polysciences, Inc.), was introduced into the multiwells and polymerised at 60°C for 48 h. The resin plus cells were detached from the culture substrate and re-embedded in Poly/Bed812 for a further 48 h. Sections were cut on a Reichart OMU4 ultramicrotome and either stained with toluidine blue for light microscopy or mounted on 300 mesh, uncoated copper grids, stained with uranyl acetate and lead citrate, before being examined in an AEI 801 electron microscope.

DETERMINATION OF CELL VIABILITY

Cell viability was determined by the trypan blue exclusion technique.[31] A 0·4% trypan blue solution was either: diluted 1:10 and placed directly on to cells attached to the substrate; or diluted 1:10 with a suspension of cells which had become detached from the substrate. One drop of the suspension was then placed on a slide and mounted with a coverslip.

Cells were examined by bright field light microscopy. Dead cells were defined as those which took up stain within 3–10 minutes of staining.

Results

All human RPE cells readily phagocytosed latex microspheres, melanin granules, lipofuscin granules, and bovine rod outer segments.

Cells grown on chamber slides showed a number of differing morphological changes which were dependent on the number of particles presented in the challenge. Observation on cultures 24 h after challenge with the highest concentrations of melanin, lipofuscin, or latex microspheres showed a massive drop-out of cells when compared with unchallenged cultures (Figs. 1 and 2). Those cells remaining were crammed full of granules and had assumed either a stellate or rounded appearance. Between 15 and 30% of these cells showed uptake of trypan blue, indicating cell death. The overlying medium was full of cell debris, and of the few intact cells in suspension all had taken up trypan blue. Cells in cultures which had received the intermediate particles concentration displayed a morphology with partially rounded profiles when compared with unchallenged cells (Figs. 1 and 2). In contrast cells in those cultures that received the lowest challenge dose retained a morphology similar to that of untreated samples (Figs. 1 and 2).

Cultures which had been challenged with bovine rod outer segments showed comparable morphological changes with increasing particle concentration, but the time period required to achieve such changes was longer. Little morphological change was apparent within 24 h of challenge (Fig. 2), but within two to three days a similar appearance was seen in those cells challenged for 24 h with melanin, lipofuscin, or latex microspheres.

A similar spectrum of morphological changes to that seen in cultures grown on chamber slides was observed in cells grown in multiwells except that in each case the time scale was extended. Cell detachment following the highest challenge concentration of melanin, lipofuscin, or microspheres did not occur until three to four days after challenge. Again cells challenged with rod outer segments took the longest time to respond, and although they rounded up they did not become detached from the substrate within the time course of the experiment (four days).

Light microscopy showed the cytoplasm of all challenged cells to be congested to varying degrees with particles, and confirmed that the cells had rounded up by reducing the length of their boundary membrane (Fig. 3). All samples of cells challenged with lipofuscin or melanin were examined by fluorescence microscopy to check for cross contamination. There was virtually no contamination of lipofuscin by melanin and only minimal (3–5%) contamination of melanin with lipofuscin. The purity of our challenges was further verified by electron microscopy.

The eye cup preparations did not provide useful results. In unchallenged specimens that were fixed immediately after dissection, and prior to incubation of fellow samples, RPE cell loss was apparent. The damage to these cells was in part due to post-mortem changes and in part due to physical disturbances induced by handling during isolation of corneal buttons for grafting. The magnitude of this non-specific cell loss rendered any analysis of further losses due to challenge impossible. These results are disappointing and in contrast to those of Feeney and Mixon.[32] However, these workers began retinal incubations within four to six hours of death, and concentrated most of their published observations on bovine RPE.

Discussion

The accumulation of any non-functional molecule or particle within a cell is a sign of increasing senescence.[12] If accumulation reaches a critical level, thus overwhelming cell renewal and/or replacement mechanisms, senescence proceeds to cell death. The progressive accumulation of lipofuscin within the human RPE cell is unique in that the major part of this waste product or debris is thought to be derived from the phagocytic load imparted by a second cell system, the photoreceptor cells. With loss of available cell volume for organelles engaged in active transport and other metabolic support roles, the decline in aging RPE cells has a rapid feedback, manifesting as a diminishing capacity to cope with the demands of the overlying photoreceptor cells. This cyclic progression may well underlie the generation of the commonest cause of retinal blindness in the

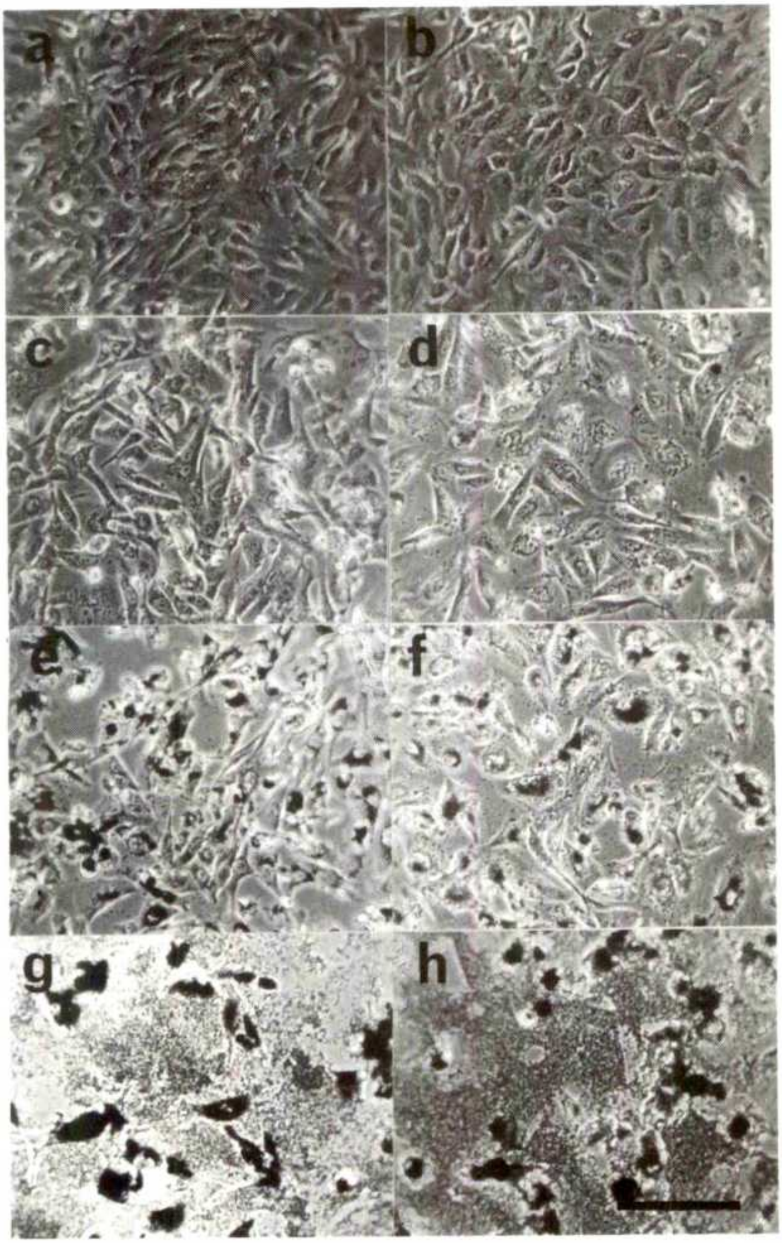

Fig. 1 *Light micrographs of human retinal pigment epithelial cells on chamber slides 24 h after challenge with concentrations of* 3×10^6 (c, d), 3×10^7 (e, f), *and* 3×10^8 (g, h) *of melanin* (c, e, g) *and lipofuscin* (d, f, h) *particles.* a *and* b *are controls and the bar marker is 200 μm. Note the progressive loss of cell-to-cell continuity.*

western world, namely senile macular degeneration.[2 33-35]

In human RPE in vivo the lipofuscin content increases with increasing age, while at the same time the number of melanin granules reduces as more and more granules are seen in melanolysosomal or melanolipofuscin complexes.[36] The former are thought to occur both as a result of slowing of the rate constants of enzymes involved in lysis of rod discs and of the progressive development of faults in those chemical reactions which result in only partially digested end products. The latter is thought to arise through an age related loss of cell enzyme specificity in which recognition of self begins to fail.

The selective distribution of high concentrations of lipofuscin within RPE cells at the macula[10] may reflect either an increased or higher phagocytic load presented to these cells by photoreceptor cells whose

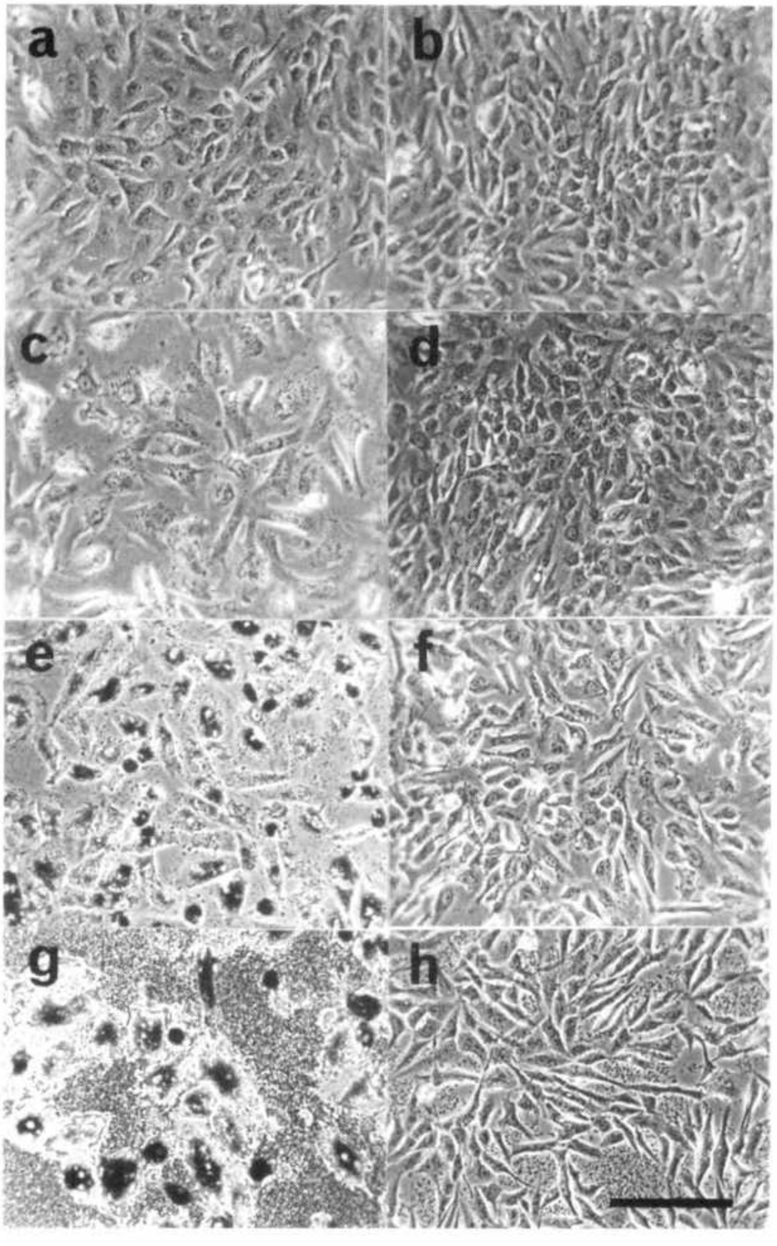

Fig. 2 *Light micrographs of human retinal pigment epithelial cells on chamber slides 24 h after challenge with concentrations of 3×10^6* (c, d), *3×10^7* (e, f), *and 3×10^8* (g, h) *of latex microspheres* (c, e, g) *and bovine rod outer segments* (d, f, h). a *and* b *are controls and the bar marker is 200 µm. Note the progressive loss of cell-to-cell continuity.*

outer segment renewal rates exceed those in other regions, or a decreased lytic or metabolic activity within this area of the RPE. At present no empirical evidence supports the concept of higher turnover rates within the outer segments of foveal cones. In contrast the recent findings of Flood *et al.*[13] showing a reduced proliferation rate in cultures of RPE cells derived from this region, and a more significant loss of activity with increasing age than that shown by cells from more peripheral regions, seems to support the second postulate, that of selectively impaired RPE.

In vitro all human RPE cells may be considered as rejuvenated in that they have recently undergone nuclear division and have shed their accumulated phagocytic load by successively sharing it between daughter cells. We have then a unique opportunity to progressively assess the senescence inducing

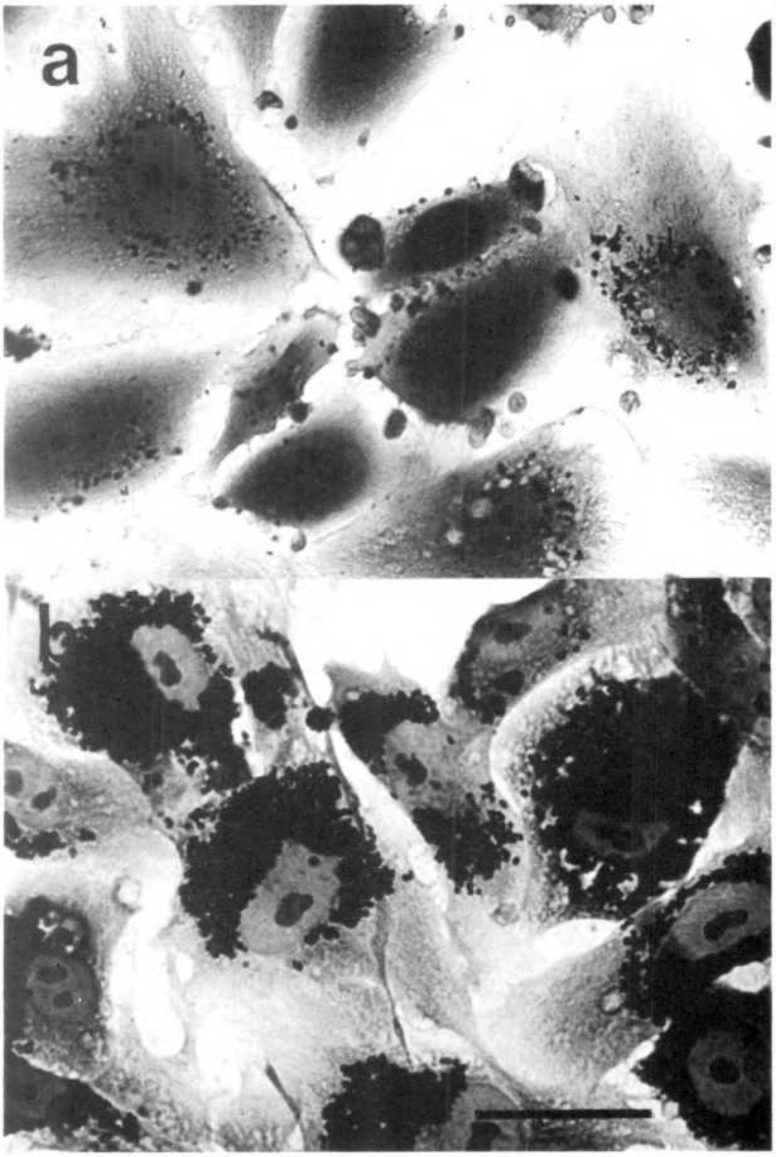

Fig. 3 *High power light micrographs of human retinal pigment epithelial cells showing the ingestion of melanin granules and the change in cell morphology as the concentration of particles in the challenge increases:* (a) 3×10^6, (b) 3×10^7. *Note the significant shrinkage of cells at the higher concentration and the greater perinuclear accumulation of melanin. The bar market is 40* μ.

capabilities of a number of different particles at varying concentrations. In future we hope to examine these selectively in peripheral and macular RPE.

The preliminary results in the present study have demonstrated that, if sufficiently high concentrations of any of our test particles were taken up over a very short time span, they all induced cell death. This would seem to imply that under our conditions the ingestion phase of phagocytosis has no feedback control from sensors of cell cytoplasmic volume, and the process continues until the cells literally burst. For useful studies of cell senescence the concentration of particle in the challenge must be carefully controlled to prevent cell rupture due to overengorging.

On the basis of accumulated evidence the assumption in this experiment was that melanin and latex microspheres would occupy cell volume, but not be digested and not be toxic. In contrast rod outer segments would initially occupy cell volume, but would be progressively reduced by lytic processes, while lipofuscin would occupy cell volume, would not be digested, and would perhaps be mildly toxic. As all but the lowest concentrations of microspheres, melanin, and lipofuscin induced profound morphological changes in the cells, we concluded that our initial challenges were too severe, or the challenge contact time was too long. However, the latency in onset for the induction of changes by challenge with rod outer segments may have been due to a limited degradation of some of the ingested particles, thus extending the time taken for cytoplasmic congestion to become apparent.

The differences observed in both time of onset and magnitude of cell detachment in relation to cells grown on the two different substrates may well be an artefact related to challenge but exaggerated by differences in adhesion, in that RPE cells always adhere more strongly to plastic than to glass.

The progressive accumulation of lipofuscin within RPE cells is thought to be implicated in a second manifestation of the aging outer retina, that of drusen formation.[37] The postulated reaction sequence[11] is that, as the aggregated load of lipofuscin reaches a critical level, the host cell makes extreme efforts to shed the lipofuscin and other lysosomal particles by voiding them into Bruch's membrane. However, Bruch's membrane also undergoes aging changes which result in an increased fibre content,[38] and therefore an increased resistance to the passage of particulate material. Extracellular debris soon begins to accumulate on its innermost aspect. Such focal excrescences expand and may resolve into one of two major types of drusen, thus becoming either dome shaped and granular or hyalinised and globular. All eyes in people over 40 have drusen at the retinal periphery.[39] In this location drusen do not lead to sight threatening consequences even though they are associated with macrophages and neovascular complexes invading the substance of Bruch's membrane.[39] In contrast, when they congregate in the posterior pole,[40] they frequently result in major decrements in retinal function[41] and senile macular degeneration.

Our model will enable the investigation of such putative interactions to be undertaken by systematically varying lipofuscin content in a number of cultures of RPE cells of different ages from various retinal locations. Further, using the current procedure in collaboration with the previously described technique for growing cultures on a permeable membrane,[23] it may be possible to study some of the processes involved in remodelling of basement membranes and drusen formation in vitro.

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Foveomacular retinitis

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SUMMARY A group of patients is described who developed the clinical features of foveomacular retinitis. No causative factors were isolated, and all patients strongly denied any type of sun gazing. It is possible that there is a group of patients who have the features of foveomacular retinitis but have not had any direct exposure to the sun. These patients would then constitute a primary type of foveomacular retinitis, as opposed to a secondary type which has a known cause and is synonymous with solar retinopathy.

Foveomacular retinitis (FMR)[1 2] is a disease involving the posterior pole of the eye in which characteristic foveal lesions develop. The term has been used synonymously with solar retinopathy,[3-5] a condition with a specific fundal appearance and associated with a characteristic history of direct gazing at the sun or observation of an eclipse. However, it has also been described in patients who have denied sun gazing.[6]

Cases

This paper describes a series of 10 patients who, while showing the features of foveomacular retinitis, did not have any history of exposure to an eclipse, direct sun gazing, or trauma. The aetiology remains unknown, and the condition does not fit into any of the categories of subtle macular changes similar in appearance to foveomacular retinitis.

The patients' ages ranged from 16 to 57. There were six females and four males. Three cases were bilateral (1 F, 2 M) and seven were unilateral (4 RE, 3 LE). The vision varied between 20/25 and 20/30. The length of history varied from a few months in the younger patients to many years in the older patients. There was no history of trauma, sun gazing, or eclipse observation. No precipitating factors were noted, and none of the patients could recollect any coexisting viral infection at the time of onset.

A uniform symptom was an inability to see the 'whole'. Letters jumped or were missing from the area being observed. The actual slight drop in vision did not disturb the patients. These findings were confirmed on Amsler grid charting, which showed small central defects in the affected eyes. The length of follow-up extended from six months to six years.

All patients were examined at least twice, with a minimum of six months between the two visits. In none, was there any alteration of the central macular area. All patients had biomicroscopy and contact lens examinations. Fluorescein angiography was performed on six patients. Two patients had a full battery of tests for uveitis. The results were negative. No peripheral fundal lesions were noted, and tonometry was normal in all patients.

The fundal area was typical, with minor variations (Fig. 1). At the macula a small red granular spot was

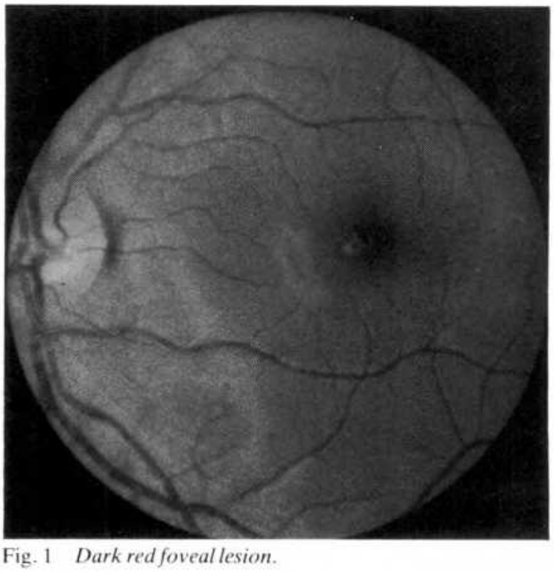

Fig. 1 *Dark red foveal lesion.*

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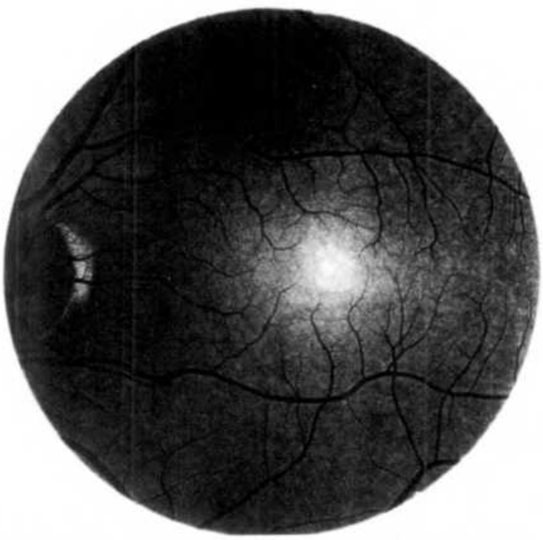

Fig. 2 *Late stage angiogram showing faint ring shaped window defect.*

noted. This might be linear or irregularly shaped. On superficial inspection it seemed to be a deep retinal haemorrhage. Closer examination showed that it was probably a small lamellar hole. It was, however, extremely difficult to be sure of the depth of the lesion. Surrounding this central area was a zone of disturbed macular pigment, with a rather mottled appearance. Irregular foveal reflexes were noted, and depending on the angle of the incident beam one or two yellowish reflexes or dots adjacent to the red spot were seen. The lesion appeared to change subtly as the incident beam of the slit-lamp was moved during contact lens examination. No evidence of serous detachment or vitreous cells were noted.

The fluorescein angiogram (Fig. 2) showed a ring of pigment epithelial damage appearing as a faint window defect. It was seen in every patient on whom an angiogram was done, and was thus unlike the lesions described in solar retinopathy, of which only severe cases show angiographic abnormalities. No full thickness foveal holes were noted.

Discussions

It is difficult to differentiate FMR from solar retinopathy, because the fundal appearance of both conditions are so similar. In solar retinopathy there is a history of recent viewing of an eclipse, or direct gazing at the sun by malingerers, sunbathers, nudists, drug addicts, and other cultists. A recent history of arc welding may also be given. Dhir *et al.*[7] grouped the fundal lesions of solar retinopathy into three clinical subgroups: mild—dark brown granular lesion at the macula without macular oedema, situated perifoveally; moderate—reddish brown granular area surrounded by a grey ring of perifoveal retinal oedema; severe—greyish white patch due to severe oedema, and situated parafoveally. The fluorescein angiogram was usually normal, but a transmission defect or microleak in the parafoveal area occurred in some of the severe cases. Retinal oedema might mask the choroidal fluorescence, and the xanthophyllic pigment of the macular area might also mask minor pigment epithelial damage.

The severe burns usually resolved into a foveomacular hole with pigment clumping and mottling. In the late state two types of holes have been described,[7] namely, a true lamellar hole due to necrosis of the inner retinal layers, and a pseudolamellar hole due to acute necrosis of pigment epithelial cells with formation of a pigment epithelial cyst. The appearance is that of a dark red or brownish hole-like lesion. It may also appear reddish-white with small yellow exudates in the centre of the lesion.[3]

The angiograms of the patients described in this series are identical to the angiograms of those patients described by Dhir *et al.*[7] as having severe solar retinopathy. His patients had variable loss of vision and were described as belonging to his severe group; despite the severity of the lesions, most recovered to 6/6 vision. The patients described here also had minimal loss of vision despite their angiographic abnormalities.

Most patients with solar retinopathy seem to recover fully or return to near normal acuity, though some cases do have a poorer prognosis.[8] Foveomacular retinitis was first described by Cordes[1] in 1944, and then by Kerr and Little in 1966.[2] All their cases were in young naval personnel, all of whom denied sun gazing or trauma. A yellowish foveal exudate developed which was surrounded by a grey zone of parafoveal oedema. After 14 days this disappeared, leaving a reddish foveal depression which became a foveal hole. The vision varied between 20/50 and 20/400, with no improvement in the cases with poor vision. Of great significance is the fact that some patients developed lesions in their second eye while confined to their ward in the hospital. Kerr and Little thought that the disease resulted from a localised choriocapillary vascular disease, with acute necrosis of the fovea.

Some authors[3,4] consider that FMR and solar retinopathy are one and the same condition. However, some 42% of their cases did not have a history of sun exposure of any type. Woldoff and Kilpatrick[6] also described three patients, all females, who strongly denied sun gazing and in whom FMR developed.

Several other conditions may mimic foveomacular retinitis; they are rare. The appearance of the lesion and a careful history will distinguish these cases from those of solar retinopathy or FMR. They include ocular contusion[9] and whiplash maculopathy[10] due to tractional forces at the vitreoretinal interface, a congenital variation of macular anatomy, toxic maculopathy, acute retinal pigment epithelitis,[11,12] and acute macular neuroretinopathy.[13,14]

In our patients the natural history was that of a sudden but minimal loss of vision. The visual loss did not vary and there was no recovery to normal. Patients adapted to this loss without difficulty. No family history was noted. All patients strongly denied exposure to an eclipse or sun gazing. The aetiology of the condition is unknown. Hereditary, known inflammatory, and traumatic influences have been excluded. It is possible that accidental exposure to excessive levels of the visible light spectrum could cause the lesions, but all patients denied such a possibility.

It would thus appear that the fundal appearances described in both FMR and solar retinopathy are identical. Two subgroups, however, seem to exist. In the first or primary type there are none of the aetiological features associated with solar retinopathy. The fluorescein angiogram shows mild abnormalities and the vision is usually around 20/30. In the second group there is a definite history of exposure to excessive levels of the visible light spectrum. Fluorescein angiographic abnormalities are usual in severe cases and, if present, may be associated with considerable loss of vision.

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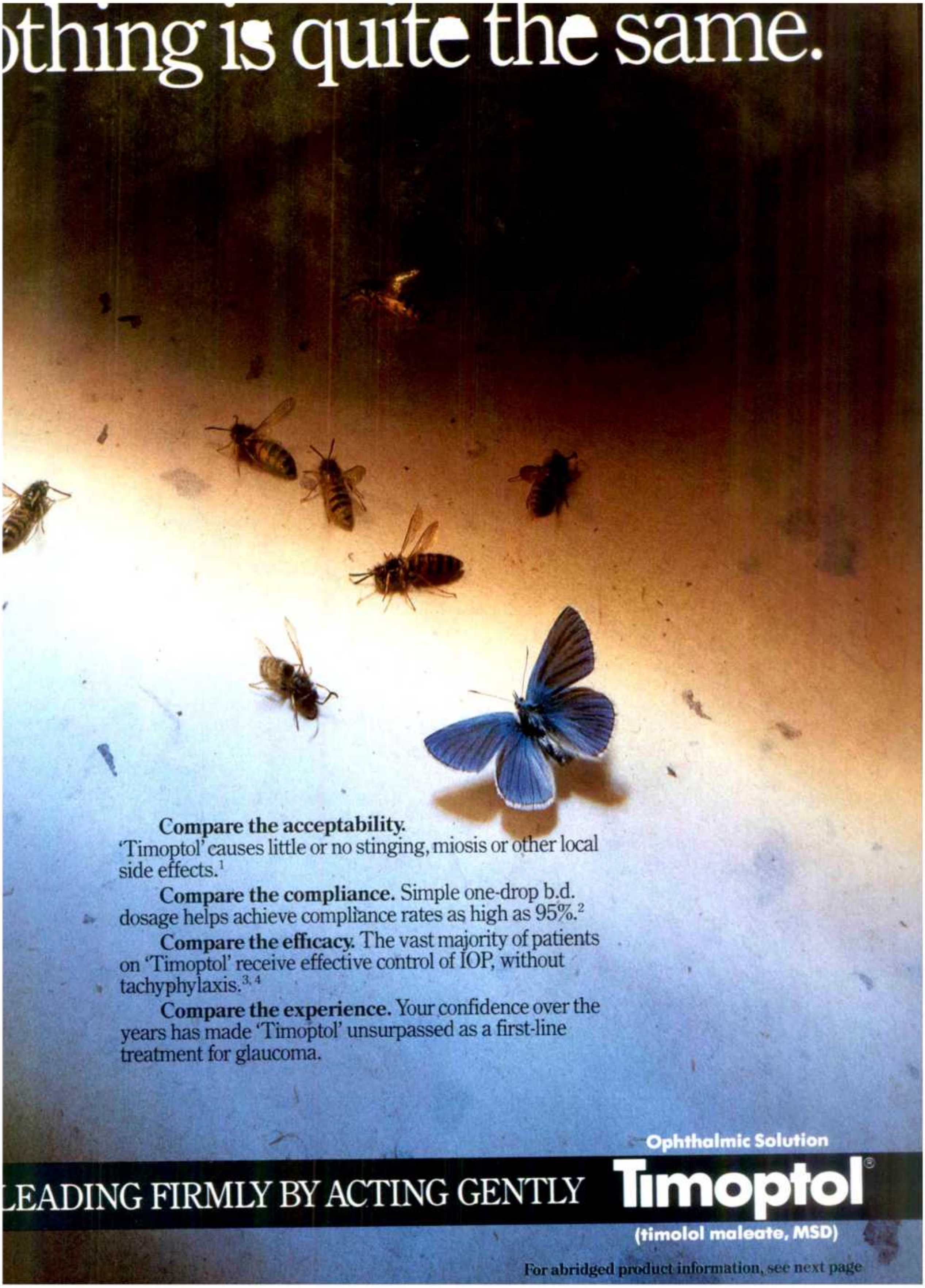

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British Journal of Ophthalmology, 1986, **70**, 819–824

Electrophysiological assessment of aphakic cystoid macular oedema

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SUMMARY Focal electroretinograms (FERG), pattern electroretinograms (PERG), and visual evoked potentials (VEP) were studied in a group of 30 aphakic patients with cystoid macular oedema (ACME). When compared with a control group of age-matched aphakics, 35% of patients were found to have abnormal FERG responses and 53%—over half of whom had normal FERG responses—showed abnormal PERG amplitudes. Although most of the patients had associated optic disc leakage, VEP latencies were normal in 26 out of 30. These results may explain the more severe visual loss seen in some ACME patients where the ophthalmologically visible retinal changes do not seem sufficient to explain such reduction in vision.

Aphakic cystoid macular oedema (ACME), originally described by Irvine[1] and Gass and Norton,[2] remains a poorly understood condition which affects from 5% to 50% of the aphakic population depending on the time at which the patient is tested.[3] Some patients improve spontaneously, whereas others develop irreversible visual loss in spite of attempted therapy.[4] Alterations in capillary permeability in the posterior segment result in leakage of fluid from the perifoveal capillaries and from the optic nerve head.[2] However, the visual loss is often not explained by the observed macular oedema, and visual acuity may vary considerably in patients with resolved macular oedema. Since most patients with ACME have a variable degree of optic disc leakage on fluorescein angiography, and often no other evidence of papillopathy (normal clinical appearance of the discs, normal fields, and pupillary responses), we attempted to determine whether subtle underlying ganglion cell or optic nerve head dysfunction might be contributing to the unexplained visual loss.

We utilised electrophysiological measures to differentiate the site and nature of the visual dysfunction in ACME patients. The localised nature of this disease necessitated the use of tests of foveo-macular function: photoreceptor and bipolar dysfunction (outer retinal layers) were assessed by means of a focal electroretinogram (FERG); inner layer neuronal (ganglion cell) disturbances were measured by a pattern electroretinogram (PERG). The visual evoked potential (VEP) was used as an indicator of the integrity of the entire visual pathway with emphasis on macular function.

Subjects and methods

Case selection and methodology. Thirty aphakic patients with postoperative development of decreased visual acuity due to ACME were studied. Disc leakage was graded as mild, moderate, or massive, the grade being based on fluorescein angiography (FA). ACME was graded from 0 to 4, the grade also being based on FA: 0=observable oedema with no macular leakage; 1=less than perifoveal oedema; 2=minimal perifoveal oedema; 3=perifoveal oedema of approximately 1 disc diameter; 4=severe perifoveal oedema.[4] An age matched group of aphakic patients with good visual results and no disc or macular oedema were selected as controls.

All subjects were refracted to their best corrected visual acuity (VA), and appropriate lenses were used during electrophysiological testing. Goldmann visual fields and pupillary responses were tested. Dilated fundus examinations including slit-lamp biomicroscopy with the Goldmann contact lens and disc were performed on all patients. Those patients with

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evidence of preoperative optic nerve disease, previous retinal detachment, macular degeneration, glaucoma, other retinal disease, corneal pathology, or a history of preoperative inflammatory eye disorder (for example, vitritis) were excluded.

FOCAL ELECTRORETINOGRAM (FERG)

Stimulus. The stimulus consisted of a tightly clustered array of red (630 nm) LEDs mounted in the rear of a ganzfeld bowl. A ground glass placed in front of the LEDs diffused the light so that it was a uniform circle of red light subtending 10° at the eye. The stimulus was sinusoidally modulated (Interstate F44) around a mean luminance of 50 cd/m^2 and at a maximum depth of 100% (i.e., 0 to 100 cd/m^2), at temporal frequencies ranging from 10 to 40 Hz. The bowl luminance was maintained at 25 cd/m^2. This level was shown in preliminary testing to eliminate activation of the peripheral retina by scattered light from the stimulus. In control experiments the amplitude of the recorded FERG response was eliminated when the stimulus was imaged on the optic nerve head, and the response amplitude grew dramatically under both central and optic nerve fixation when the background light was turned off. After the pupil was dilated with 1% tropicamide (Mydriacyl) the patient placed his head in a ganzfeld bowl and fixated the centre of the LED array.

Recordings. FERG responses were recorded by means of a gold foil electrode[5] hooked over the lower lid and referenced to the ipsilateral ear. The contralateral ear served as earth. The fellow eye was patched in all tests.[6] The electrical signal was amplified by a Grass P511J preamplifier (gain= 10 000) with bandpass filter settings appropriate to the frequency of stimulation. The amplified signal was summed (n=128) on a Nicolet 1170B signal averager. Any sweeps containing large amplitude potentials due to blinks or eye movement were eliminated from the averaged response by setting the artefact rejection control of the Nicolet to an appropriate level. The averaged responses were then recorded on an X-Y plotter for later analysis.

PATTERN ELECTRORETINOGRAM (PERG)

Stimulus. A black-and-white checkerboard, reversing position 11 times/s, was generated on a Conrac video monitor (model QQA 14-N) by an Institute of London (T221) pattern generator. Each check subtended 1° of visual arc/side, and the entire pattern on the television screen measured 16×23°. Average mean luminance of the display was set at 50 cd/m^2 and the pattern contrast was 50%. These parameters have been shown by previous work to produce the largest PERG response in normal persons.[7]

Recordings. The PERG responses were monocularly recorded with a gold foil electrode. Signals from the eye were amplified and averaged in the same manner as the FERG responses.

VISUAL EVOKED POTENTIALS (VEP)

Stimulus. The same stimulus apparatus used for PERG stimulation was used to generate VEP responses. Check size was reduced to 1/2°, reversal rate slowed to 1·5 rev/s for transient potentials, and the screen was moved away from the subject and subtended 8×11·5°. For recording the steady state VER the reversal rate was increased to 11 rev/s and the contrast lowered to 6·0%.

Recordings. A gold cup electrode was positioned 2·5 cm above the inion and referenced to the right ear lobe. The left ear lobe served as earth. The amplification and averaging remained the same as in the PERG and FERG. The latency of the transient response was measured as the time from stimulus onset to the peak of the first prominent positive wave (P100). Steady state response amplitude was measured from the most negative portion of the wave to the top of the following positive peak.

Results

Control subjects. Seventeen aphakic subjects (26 eyes), ranging in age from 40 to 85 years (mean 66·9), were studied. Best corrected visual acuities in this group ranged from 20/20 to 20/30 with a mean of 20/25. Twelve eyes had intracapsular cataract extractions (ICCE), seven of which had intraocular lenses (IOL) (one iris clip and six anterior chamber lenses (AC)). Ten eyes had extracapsular cataract extractions (ECCE), eight of which had posterior chamber (PC) IOLs. The 11 controls without IOLs required high plus lenses (i.e. >+10 dioptres for correction).

ACME patients. Thirty ACME patients (33 eyes), ranging in age from 57 to 86 years (mean 72·4) and with visual acuities ranging from 20/20 to 20/200, with a calculated mean of 20/94, were tested. The distribution and duration of macular oedema and optic disc leakage in these patients is shown in Table 1. Twenty-seven of the 33 eyes had optic disc leakage associated with macular oedema. Five eyes had optic disc leakage with grade 0 macular oedema, and two eyes had macular oedema with no disc leakage.

Four eyes with prior leakage on fluorescein angiography had no leakage or macular oedema at the time of electrophysiological testing: patient 30 (Table 1) had prior ACME grade 3 and massive disc leakage of eight months' duration; patient 31 had prior ACME grade 1 and mild disc leakage of 12 months' duration; patient 32 had prior ACME grade 2 and moderate disc leakage of 4·5 months' duration; and patient 33

Table 1 *Clinical profiles of ACME patients and comparisons among electrophysiological tests (●=abnormal response)*

	Age	*Sex*	*Eye*	*VA*	*Procedure*	*IOL*	*Vitrectomy*	*CME grade*	*Optic disc leakage*	*Duration (months)*	*VEP latency*	*VEP amplitude*	*PERG*	*FERG*		
														10	*30*	*40*
1	58	M	OS	60	ECCE	PC	No	2	Massive	5			●			
2	64	F	OD	200	ICCE	No	No	1	Massive	16	●	●	●			
3	86	F	OD	100	ICCE	IC	No	4	Moderate	11		●				
4	59	F	OD	30	ICCE	No	No	3	Moderate	11			●			
5	67	F	OD	30	ECCE	PC	No	3	Moderate	1			●			
6	83	F	OS	60	ICCE	AC	No	2	Moderate	1						
7	72	M	OD	200	ICCE	No	No	2	Moderate	5		●				●
8	66	F	OD	70	PHACO	PC*	No	1	Moderate	10			●			
9	57	M	OD	25	ICCE	No	No	0†	Moderate	4						
10	57	M	OS	50	ICCE	No	No	1	Moderate	4						
11	76	M	OS	200	ECCE	AC*	No	4	Mild	2·5	●	●	●			
12	55	F	OD	100	ECCE	No	Yes	4	Mild	5						●
13	57	F	OD	200	ECCE	No	No	3	Mild	2			●			●
14	76	M	OD	80	ICCE	No	No	2	Mild	6	●	●	●		●	●
15	76	M	OS	80	ICCE	No	Yes	3	Mild	6	●	●		●	●	●
16	60	F	OS	200	ICCE	No	No	1	Mild	12	●		●			
17	73	F	OD	200	ICCE	IC*	Yes	1	Mild	2			●			●
18	70	F	OD	70	ICCE	AC	No	1	Mild	5						
19	73	F	OD	25	ICCE	No	No	0†	Mild	36			●			
20	75	M	OS	100	ICCE	AC	No	3	Mild	3		●	●			●
21	67	M	OD	200	ECCE	AC	No	2	Mild	5·5						
22	81	M	OD	100	ECCE	PC	No	2	Mild	1			●		●	●
23	82	F	OS	200	ECCE	AC	No	1	Mild	4			●		●	●
24	84	F	OD	100	ICCE	IC	No	0†	Mild	12		●				
25	84	F	OS	100	ICCE	IC	No	0†	Mild	12		●	●			
26	76	F	OD	100	ICCE	AC	No	0†	Mild	9						
27	53	M	OS	30	ICCE	No	No	1	Mild	6		●	●			
28	74	F	OS	25	ICCE	No	No	2	None	11						
29	61	F	OD	40	ICCE	AC	No	2†	None	1·5						
30	61	F	OD	40	ICCE	AC	No	0†	None	8						
31	77	F	OD	25	ICCE	No	No	0†	None	12						
32	71	F	OD	25	ECCE	PC	No	0†	None	4·5						
33	73	F	OD	50	ICCE	IC	No	0†	None	8			●			●

IC=Iris clip. *Lens Removed. †Grade 0 ACME at the time of testing (see text for prior extent).

had prior ACME grade 2 and mild disc leakage of eight months' duration.

Twenty-three of the eyes had intracapsular extractions, 12 with IOLs (five iris clip), one of which required removal, and seven AC lenses). Nine eyes had extracapsular extractions—four with PC IOLs and three with AC IOLs, one of which required removal. One eye had a phacoemulsification (PHACO) with a PC lens which required removal. Three of the 33 eyes had vitrectomies (two ICCE and one ECCE). Seventeen patients' eyes required high plus lenses for correction. The appearance of the optic nerve head by Goldmann contact lens examination, Goldmann visual fields, and pupillary responses were normal in 31 of 33 eyes. One patient (Table 1, No. 2) had severe postoperative ischaemic papillopathy (4+ hyperaemic disc and massive optic nerve head leakage), with an afferent pupillary defect and a residual 3° visual field; another patient (No. 11) also sustained a postoperative ischaemic papillopathy with disc pallor, an altitudinal visual field loss, and an afferent pupil defect.

There was low correlation between the grade of macular leakage and visual acuity, the grade of disc leakage and visual acuity, and the duration of leakage and visual acuity (Table 2).

ELECTROPHYSIOLOGICAL RESULTS

Controls. The electrophysiological data of the controls tested with high plus lenses were not significantly different from those having IOLs. Likewise the data for ICCE versus ECCE controls were not found to be significantly different. Therefore the data from all controls were grouped for further analysis. Focal ERG amplitudes for 10 Hz averaged 7·8±3·6 μV, for 30 Hz 5·4±2·5 μV and for 40 Hz 5·6±1·6 μV. Control FERG amplitudes ranged from 3·2 to 14·8 μV at 10 Hz, 2·2 to 10·9 μV at 30 Hz, and 3·2 to 9·2 μV at 40 Hz. Pattern ERG amplitudes at 50% contrast for this series averaged 8·7±3·3 μV. The range of PERG amplitudes in this group was from 4·5 to 17 μV, and the interocular difference in amplitude averaged 1·2±0·6 μV. The mean VEP latency for the controls was 104·5±10·1,

Table 2 *Correlation coefficients between clinical and electrophysiological measures in patients with ACME*

	Duration	*VA*	*CME grade*	*Optic disc leakage*	*VEP latency*	*VEP amplitude*	*PERG*	*FERG*		
								10	*30*	*40*
Duration	1·0	−0·19	−0·30	−0·17	−0·12	0·24	−0·09	0·16	0·26	−0·02
VA		1·0	0·25	0·30	0·17	−0·34	−0·41	−0·19	0·38	0·04
CME grade			1·0	0·37	−0·02	−0·24	−0·01	−0·36	−0·27	0·03
Disc leakage				1·0	0·21	−0·57	−0·33	−0·27	−0·18	0·18
VEP latency					1·0	−0·36	−0·30	−0·23	−0·06	−0·30
VEP amplitude						1·0	0·24	0·33	0·20	0·13
PERG							1·0	0·11	0·21	0·03
FERG 10 Hz								1·0	0·54	0·16
FERG 30 Hz									1·0	0·16

with a range of 90 to 131 ms. The mean steady state VEP amplitude at 6·0% contrast was 8·6±2·9 µV. Steady state VEP amplitude ranged from 3·8 to 20·2 µV in this control group. None of the electrophysiological measures differed from those of a second control group of nine age matched aphakic normal persons.

ACME patients. The electrophysiological results of the aphakic patients with ECCE and ICCE, and those with or without IOLs, did not differ significantly and were combined for further analysis. 3% (1/31) of the FERG amplitudes at 10 Hz, 16% (5/31) at 30 Hz, and 36% (11/31) at 40 Hz were found to be below the range established by the control group.

Seventeen of 32 eyes (53%) had PERG amplitudes below the control range. Of these, eight had unilaterally absent PERG responses and the remaining nine had a mean interocular difference in amplitude of 4·6±1·7 µV. Eight of 17 had both abnormal FERG and PERG responses, and nine of 17 had only abnormal PERG responses. Those patients with only abnormal PERG amplitudes had a calculated mean visual acuity of 20/98, whereas those with both tests abnormal had a calculated mean visual acuity of 20/123. This difference was not statistically significant. The difference in the PERG response, therefore, was not related to reduction in visual acuity in this group. It is also interesting to note that the patient group with only abnormal PERG responses had a significantly longer mean duration (11·8 months) than the other ACME patients.

Only four patients (five eyes) had prolonged latencies (>131 ms). Two of these patients (Table 1, patients 2 and 11) sustained postoperative ischaemic papillopathy with visual field defects, afferent pupillary defects, and optic nerve head changes. The third patient had slightly prolonged latencies (133 ms) in both eyes with normal pupillary responses, normal visual fields, and normal optic discs. The fourth patient, likewise, had slightly prolonged latency (136 ms) with normal pupillary responses, visual fields, and optic discs.

Ten of 31 (32%) of the ACME eyes had steady state VER amplitudes below the control range.

A correlation matrix showed little relationship between the grade of macular oedema and a single electrophysiological result, between the grade of disc leakage and the electrophysiological results, or between duration of oedema and the electrophysiological results (Table 2). However, of the four patients with no leakage (disc or macula) at the time of testing three had normal electrophysiological findings. The remaining patient had persistent visual loss (20/50) and abnormal electrophysiological results.

Discussion

The major findings of this study were: (1) focal electroretinogram amplitudes were abnormal in 35% of the patients tested who had aphakic cystoid macular oedema; and (2) pattern electroretinogram amplitudes were abnormal in 53% of ACME patients, with over one-half of these patients having no associated FERG abnormalities.

The focal electroretinogram is a specific test of the temporal responsiveness of the central 10° of retina, and, like the flash electroretinogram b wave, the presence of a FERG response requires integrity of the outer retinal layers and particularly Mueller cell function.[8] Certain macular diseases have been shown to be associated with reduced FERG amplitudes. The deficits are initially observed at the higher temporal frequencies and involve the lower frequencies as visual acuity decreases.[9] Thus, for example, in Stargardt's disease with visual acuity between 20/60 and 20/100 the FERG response is absent at all temporal frequencies.[9]

Histological studies of human CME eyes have shown pathological changes occurring predominantly in the outer retinal layers, namely, accumulation of fluid in Henle's outer plexiform layer and in the bipolar neural layer,[2,10-12] photoreceptor cell dropout, and Mueller cell swelling and necrosis in the outer retinal layers.[10] Our findings of FERG reduction in ACME patients supports these prior histopathological findings.

Recently the PERG has been shown to reflect inner retinal layer function. Maffei and Fiorentini[13] showed a marked reduction of PERG amplitude and preserved diffuse flash ERG amplitude some weeks after section of the cat optic nerve and after ischaemia caused by temporary blockage of the retinal artery. The clinical importance of the PERG lies in the fact that it has been shown to be abnormal in diseases in which the optic nerve is primarily or secondarily affected and where the flash ERG is normal. In patients with severe visual loss and poor acuity caused by optic neuritis, ischaemia, or compression of the nerve no PERG response has been found in spite of normal flash ERG responses.[14-16] These findings support the hypothesis of an inner retinal layer origin for the PERG.

Seventeen of 31 (53%) of the ACME eyes in our study had abnormal PERG amplitude. These patients fell into two groups: nine of the 17 eyes had normal FERG responses and abnormal PERG responses, and eight of the 17 showed abnormalities in both responses. FERG reduction itself may cause a reduced PERG, since the functioning of the inner layers must reflect the quality of the input from the outer retinal layers. However, a large number of these patients had normal outer retinas as reflected in their normal FERG responses. In the presence of a normal FERG, PERG abnormalities must solely reflect inner retinal layer dysfunction. Although most of the visible pathological changes have been described as occurring in the outer retina, it appears that perifoveal capillary leakage and optic disc leakage may additionally cause significant changes in inner retinal layer physiology. A recent histological analysis of a human CME (not aphakic) eye reporting swollen mitochondria in optic nerve ganglion cells and swelling of the associated glial cells[17] provides supportive evidence for a lesion of the inner retinal layer in ACME.

Since most patients with ACME have associated disc leakage in addition to macular oedema on fluorescein angiography, we used the VEP to test latency in these individuals. VEP latencies have been shown to be prolonged in cases of optic neuritis of demyelinating origin, ischaemic or compressive optic nerve disease, or optic atrophy.[18 19] Although 27 of 33 eyes examined in this study showed some degree of optic disc leakage, only four patients had delayed VEP latencies. Two of these patients had severe postoperative ischaemic papillopathy, with associated visual field loss, afferent pupillary defects, one with optic disc pallor, and the other with 4+ disc hyperaemia. Thus there is rarely significant change in the conduction pathway of the optic nerve associated with optic disc leakage in ACME.

The steady state VEP has been previously used as a sensitive assay of the processing of spatial contrast information.[20] VEP contrast deficits with normal Snellen acuities have previously been demonstrated with the VEP.[21 22] 32% of the patients in this study showed abnormal VEPs at low contrast when compared with matched controls. These findings, however, can be used only as indicators of non-specific visual loss, since patients with both macular disease[23] and optic neuropathy[21] have been shown to have abnormal steady state VEP responses.

We found poor correlation between the electrophysiological results and the grade of macular leakage, or the duration of leakage, or the visual acuity. Similarly we found little correlation between visual acuity and disc leakage, or between visual acuity and ACME grade. These low correlations probably represent the limitations of the measurements. ACME grade and disc leakage may fluctuate, and the grade assigned at any particular time may not reflect the past extent of the leakage. Likewise duration alone does not reflect the severity of the pathology. For example, patients 30–33 had no leakage (disc or macula) at the time of testing, whereas all had prior clinical ACME of varying severity. Higher correlation may be found if the entire time course of the disease (including these fluctuations in degree) in a particular patient are included.

CONCLUSIONS

In addition to the obvious outer retinal layer pathology described by histological study and confirmed in the present study by abnormal FERG findings we found PERG abnormalities in a large number of ACME patients. These results suggest additional unobserved pathology involving the inner retinal layers in aphakic cystoid macular oedema, a disorder which has previously been thought of as predominantly an outer retinal dysfunction. This may explain the more severe visual loss seen in some patients where the ophthalmologically visible retinal changes do not seem sufficient to explain such reduction of vision.

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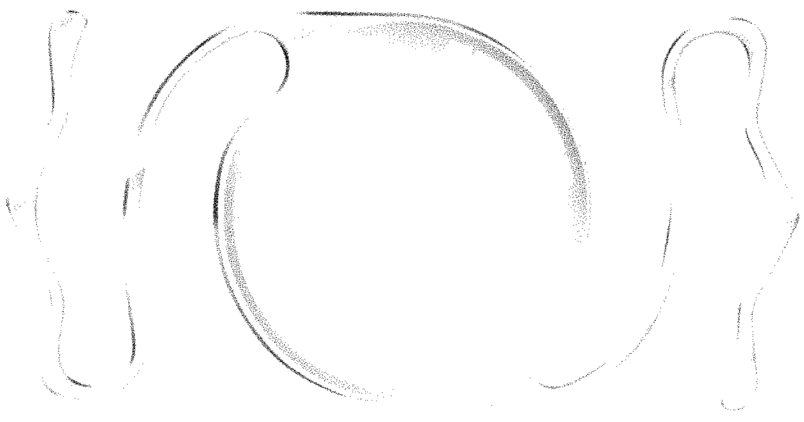

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Corneal astigmatism following cataract extraction

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SUMMARY The changes in corneal curvature in the first six months after cataract extraction were studied by performing sequential keratometry on a group of 57 patients. 8/0 Virgin silk interrupted sutures were used for the closure of corneoscleral incisions, and 10/0 monofilament tied in double running (bootlace) or single running (continuous) fashion was used for corneal wound closure. A high degree of with-the-rule astigmatism was evident in all patients two weeks postoperatively, but thereafter the character of the astigmatism produced by 8/0 virgin silk and 10/0 monofilament closure was quite different: in the 8/0 virgin silk group there was an early and pronounced shift in the axis of astigmatism to against-the-rule, whereas in the 10/0 monofilament group there was little further change in the astigmatism unless the sutures were removed. Wound compression and wound gape as factors responsible for these changes are discussed.

Astigmatism resulting from cataract extraction has been the subject of many studies. Wound gape occurring with absorbable sutures and wound compression occurring with non-absorbable sutures have been proposed by Jaffe and Clayman[1] as the prime factors responsible for changes in the corneal curvature following cataract extraction, whereas in other studies attention has been directed to factors such as length and shape of section and material and method of suturing.[2-6]

A further source of confusion is that many authors use only postoperative keratometry readings to discuss the effects of surgery, not taking into consideration that corneal curvature after cataract extraction is dependent on the preoperative corneal curvature as well as the change induced by surgery. Jaffe and Clayman[1] were the first to report exact quantitative differences between pre- and postoperative corneal curvature. They showed how the difference between these two values can be calculated mathematically and therefore provide a measure of change induced by surgery—the surgically induced astigmatism (SIA).

The aim of our study was to document the changes in corneal curvature occurring after cataract extraction over a six-month period. We planned to compare the SIA produced by closure of cataract sections with 10/0 monofilament and 8/0 virgin silk, and relate the changes in corneal curvature to wound healing, removal of monofilament, and signs of biodegradation of virgin silk. By choosing these materials we felt that the differing effects attributable to wound gape and wound compression might be more readily evident.

Materials and methods

All patients undergoing cataract extraction for senile cataract in a four-month period were included. Patients were allocated in turn and consecutively to one of the following three groups:

(1) Limbal (L). In this group cataract extraction was performed via a mid-limbal section of approximately 160° under a short limbus based conjunctival flap. The section was closed with six interrupted 8/0 virgin silk sutures, two preplaced and four postplaced.

(2) Bootlace (B). In this group a corneal section of 160° immediately anterior to the limbal vessels was made. The section was closed with a continuous double row of 10/0 monofilament sutures tied at one end of the section (bootlace fashion) (Fig. 1(B)).

(3) Continuous (C). In this group a corneal incision was made as in group B, but closure was with a single row of 10/0 monofilament suture tied in the wound at both ends of the section (Fig. 1(C)).

The section was thus of a standard length and shape in all three groups, the only difference being the mid-limbal position of the incision in group L and

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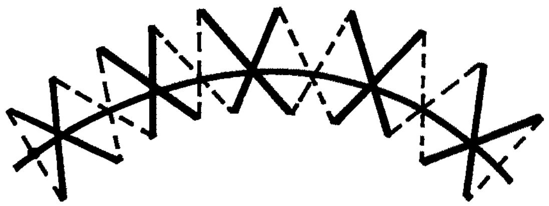

Fig. 1(B) *Diagram of continuous double row of 10/0 monofilament suture used to close a corneal cataract section (bootlace fashion).*

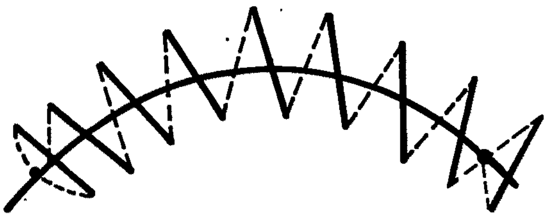

Fig. 1(C) *Diagram of continuous single row of 10/0 monofilament suture used to close a corneal cataract section.*

the corneal position in groups B and C. In all cases the section was cut vertically downwards with a razor fragment and completed with corneal scissors.

The surgery was performed by one of two surgeons —the consultant and the resident of the firm. The operating microscope was used in every case. Extracapsular cataract extraction was performed in all but three cases in which intracapsular cataract extraction was performed. A modified J loop Sinskey-type posterior chamber intraocular lens was implanted when clinically indicated. Both surgeons used all three types of incision and closure, and no patient was selectively allocated to any particular group. Any patient with previous anterior segment surgery or with any pre-existing eye disease other than cataract was excluded.

Corneal astigmatism was measured with a Topcon keratometer by an observer not involved in the surgery and without prior knowledge of the type of surgery or the surgeon involved. Keratometry was performed immediately preoperatively (K1) and postoperatively (K3) at 2, 6, 13, and 26 weeks. The law of sines and cosines[1] was used to calculate K3 minus K1 to give K2, the SIA, for each patient at each

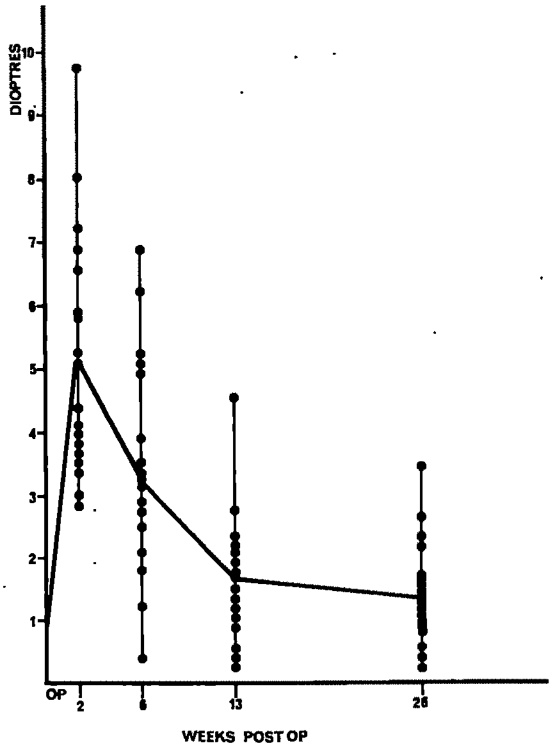

Fig. 2(L) *Changes in power of surgically induced astigmatism during the first six months following surgery in group L with limbal section and virgin silk sutures. Solid circles represent individual patients.*

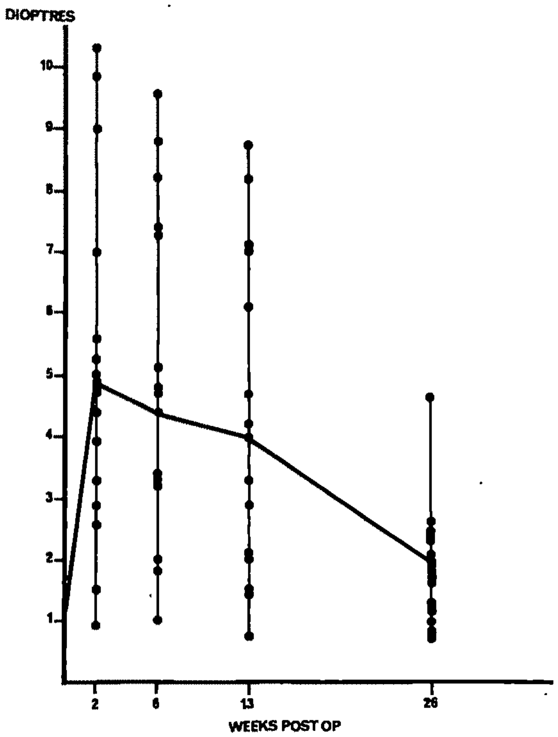

Fig. 2(B) *Changes in power of surgically induced astigmatism during the first six months following surgery in group B with corneal section and bootlace suture. Solid circles represent individual patients.*

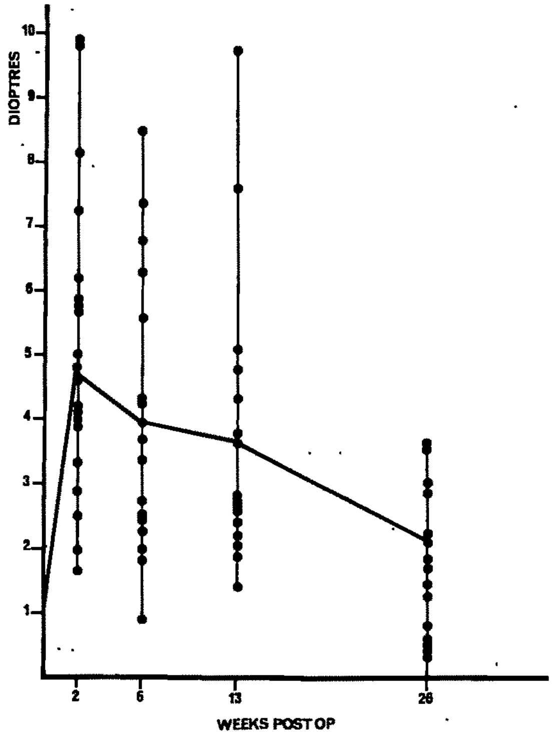

Fig. 2(C) *Changes in power of surgically induced astigmatism during the first six months following surgery in group C with corneal section and continuous suture. Solid circles represent individual patients.*

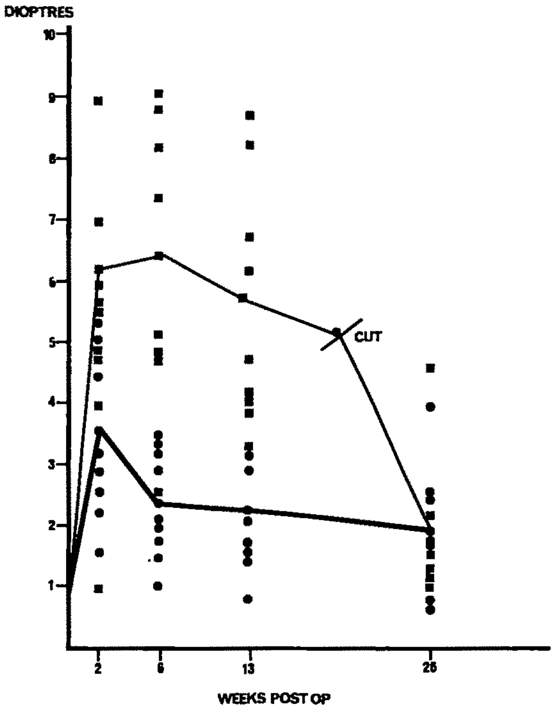

Fig. 3(B) *Changes in power of surgically induced astigmatism in group B, with those who retained their sutures represented by solid circles and those who underwent ROS represented by squares.* CUT *indicates the time of ROS.*

visit. Monofilament sutures were removed after four months if an unacceptably high degree of postoperative astigmatism was present.

Results

Fifty-seven patients were entered in the study, but two had to be withdrawn, because owing to ill health they could not attend at the required times for follow up. Seventeen patients were included in group L, 19 in group B, and 19 in group C.

POWER OF ASTIGMATISM

The change in power of SIA for each of the three groups in the first six months following surgery is shown in Fig. 2. The power of SIA is given in dioptres.

These three graphs show that, although at two weeks the power of SIA was very similar in all three groups, at six and 13 weeks a steep fall in power of SIA had occurred in group L but only a slight reduction in power of SIA in groups B and C. The reduction in power of SIA in group L between 13 and 26 weeks was only very slight, whereas groups B and C both showed a much larger drop in power of SIA over this period. However, when the patients in groups B and C are divided into those who retained their sutures and those who had their sutures removed (ROS) (Figs. 3B and 3C), we see retention of sutures was associated with near constancy of SIA, and ROS was associated with a dramatic reduction of power of SIA.

AXIS OF ASTIGMATISM

The axis of SIA is given as the plus cylinder necessary to correct the induced corneal change. With-the-rule astigmatism is defined as that which is corrected by a plus cylinder at 90°±30°,[7] against-the-rule astigmatism as that which is corrected by a plus cylinder at 180°±30°, the remaining 60° representing oblique astigmatism.

The changes in axis of SIA occurring in each group over the six-month period are shown in Figs. 4 L, B, and C. In the limbal group there was a marked change from predominantly with-the-rule to predominantly against-the-rule between weeks two and 13. In groups B and C the axis of astigmatism was predominantly with-the-rule and showed little

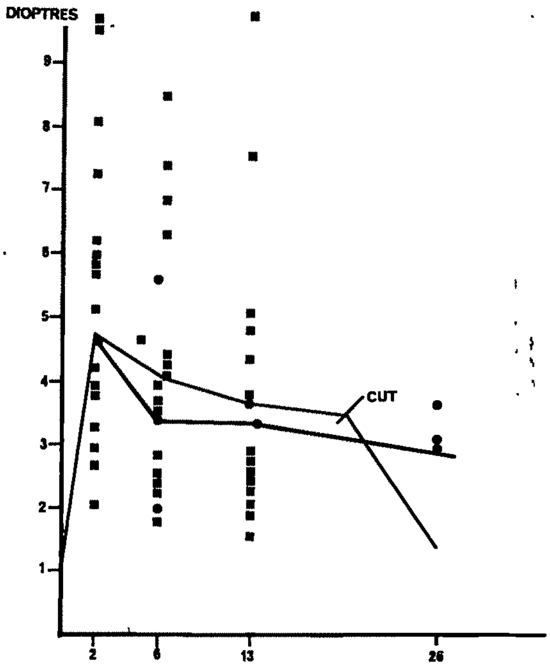

Fig. 3(C) *Changes in power of surgically induced astigmatism in group C, with those who retained their sutures represented by solid circles and those who underwent ROS represented by squares.* CUT *indicates the time of ROS.*

change over the first 15 weeks. ROS was carried out after four months, and Fig. 4 shows that ROS was associated in group B with a marked change in the axis of astigmatism. This change was not so marked following ROS in group C, possibly because there was a greater number of patients with oblique astigmatism in this group.

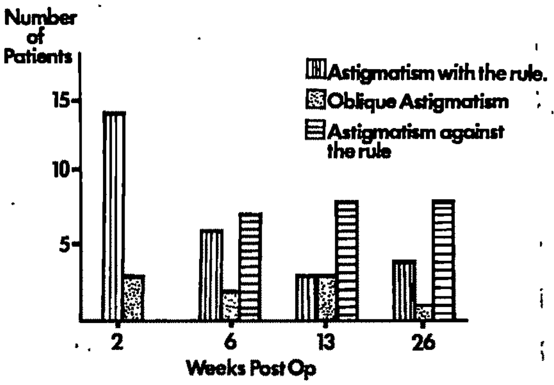

Fig. 4(L) *Changes in the axis of surgically induced astigmatism during the first six months following cataract extraction in patients who underwent a limbal section: group L.*

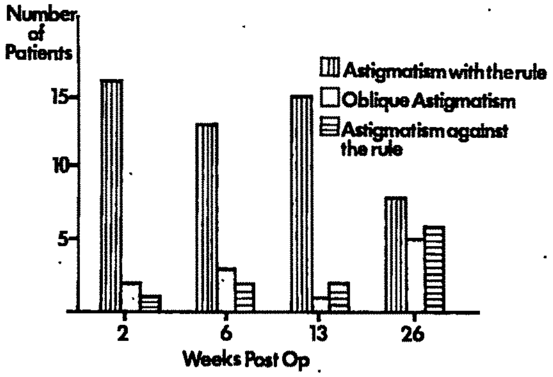

Fig. 4(B) *Changes in the axis of surgically induced astigmatism during the first six months following cataract extraction in patients who underwent a corneal section closed with a double row of 10/0 monofilament suture tied at one end of the section (bootlace fashion): group B.*

SUTURES

It was evident that those patients who had had a corneal section had much quieter eyes postoperatively than the limbal section group sutured with 8/0 virgin silk. During the early stages of healing in the limbal group an increased amount of inflammation at the wound is to be expected because of the additional surgical trauma to the conjunctiva caused by this method. In seven of the limbal group this marked inflammation settled in the course of time, but in 10 patients a persistent redness and infiltration around the sutures associated with a marked papillary conjunctivitis was noted. This reaction did not respond to treatment with topical prednisolone 1% but did settle quickly when the virgin silk sutures were removed. ROS of virgin silk was not associated

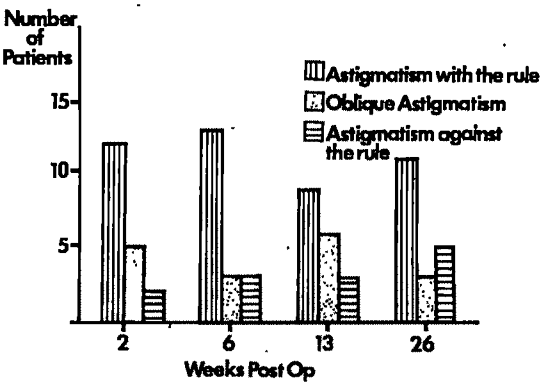

Fig. 4(C) *Changes in the axis of surgically induced astigmatism during the first six months following cataract extraction in patients who underwent corneal section closed with a single continuous row of 10/0 monofilament suture: group C.*

with any appreciable change in power or axis of SIA. Two patients in group L, both of whom had a severe inflammatory reaction to virgin silk sutures, developed peripheral anterior synechiae (PAS) noted at the six weeks visit which were not present at the two weeks follow-up visit. No other patient in this study developed PAS.

In group B monofilament sutures were associated with an unacceptably high degree of SIA in 10 patients (52·6%), and ROS was necessary to reduce this astigmatism. In group C 11 patients (57%) required ROS to reduce astigmatism. In addition in group C five patients (26%) required ROS to relieve irritation associated with broken or loose sutures. None of these patients with broken or loose sutures developed a wound leak.

Removal of the bootlace suture, when necessary, was more easily accomplished than removal of the single running continuous suture, as the single buried knot of the bootlace could be more easily pulled out of the section than the two closed loops of the tied ends of the single running suture.

Discussion

To the surgeon interested in reducing postcataract astigmatism a bewildering amount of advice on achieving this goal appears in the ophthalmic literature. Among the subjects of attention in this respect have been: the length of the section,[2] the number of sutures,[8 9] prevention of sideways shift of the wound,[4] variation in the suturing technique,[3 6 10] the use and value of the operative keratometer,[11–13] and the distance of the section from the limbus.[14] These studies show that different factors affect the change in corneal curvature following cataract extraction, but controversy surrounds their relative importance. We consider that the changes and similarities of SIA which occurred in our three groups of patients can be explained by the occurrence of wound gape and wound compression in the healing of cataract wounds.

At two weeks the results for all three groups were very similar. All three groups at this stage showed a high degree of SIA, axis with the rule, or less commonly, oblique. Despite the similarity at two weeks, at the six weeks and 13 weeks visits group L had become very different from groups B and C. Group L showed a marked reduction in power of SIA and a marked change of axis from with to against the rule. Groups B and C showed only a small reduction in power over this time and retained their axis orientation. It is apparent, therefore, that a factor common to all three groups at two weeks is no longer evident at six and 13 weeks. It would appear that the 10/0 monofilament suture holds the wound stable, whereas the 8/0 virgin silk allows a marked change in the corneal curvature to develop over the weeks in which healing is taking place. Wound compression in the first two weeks postoperatively would be similar for all three groups. Tight sutures and wound oedema would result in reduction in the radius of the curvature of the vertical meridian and astigmatism with the rule. The occurrence of oblique astigmatism at this stage can also be explained by wound compression—the meridian in which the sutures are tightest being that of the shortest radius of curvature.

Jaffe and Clayman's explanation for the occurrence of astigmatism against the rule is that, when absorbable sutures and large diameter sutures that are intended to be removed are used, wound gape occurs, and this increases the circumference of the globe in the meridian perpendicular to the line of the incision and therefore flattens the vertical meridian.[1] Virgin silk is classed as a non-absorbable suture,[15] and the 8/0 diameter sutures used in this study were not intended to be removed. However, biodegradation of virgin silk does occur,[16] and in our study this was evident from the large number of patients who required ROS for relief of suture related inflammation. It is also possible that the development of PAS in two patients was due to inflammatory reaction and wound gape related to the virgin silk sutures. Change to against-the-rule astigmatism associated with extrusion of 8/0 virgin silk has also been reported by Luntz and Livingstone.[17] Adverse reactions to virgin silk have been reported by Soong and Kenyon, who suggest that an immunological reaction mounted against the sericin gum of the virgin silk may occur.[18]

Further evidence in support of wound compression by monofilament sutures is shown by their removal. A dramatic fall in the power of SIA occurred in groups B and C in those patients who underwent ROS. A large change in the axis of astigmatism was also seen in many patients following ROS. The reduction of astigmatism following removal of monofilament sutures in corneal sections has been reported by others.[1 18 19]

In reviewing our results we were surprised at the large variation in power of astigmatism produced in our bootlace group (Fig. 3(B)). In producing a watertight closure of the section we believed we were tightening our sutures to a similar degree, yet 52·6% of group B showed a considerably higher degree of SIA. Hyde and Maumenee have pointed out that with bootlace closure, if longer bites than necessary are taken, considerably more tissue is subjected to compression by the suture.[20] The occurrence of a small percentage of patients in groups B and C who showed against-the-rule astigmatism might be explained by a mechanism proposed by Hyde.[21] He suggests that, if monofilament is used and wound gape is allowed to occur during suturing, scar formation will develop and increase the circumference of the globe, thus flattening the cornea in the meridian perpendicular to the section.

The variation in power and axis of astigmatism associated with the clinical picture of wound inflammation and suture extrusion in the 8/0 virgin silk group was in marked contrast to the constancy of power and axis of astigmatism in those patients with 10/0 monofilament closure. Furthermore, the marked reduction in SIA following removal of 10/0 monofilament showed the importance of tension in the monofilament as a cause of SIA. We consider, therefore, that wound compression and wound gape, as proposed by Jaffe and Clayman in 1975,[1] are the most important determinants of corneal astigmatism after cataract surgery, and these factors should be taken into account in any discussion of the parameters thought to influence postcataract astigmatism. We also agree with the findings of Stainer *et al.*[19] that the appropriate choice of suture material helps the surgeon to control postoperative corneal astigmatism.

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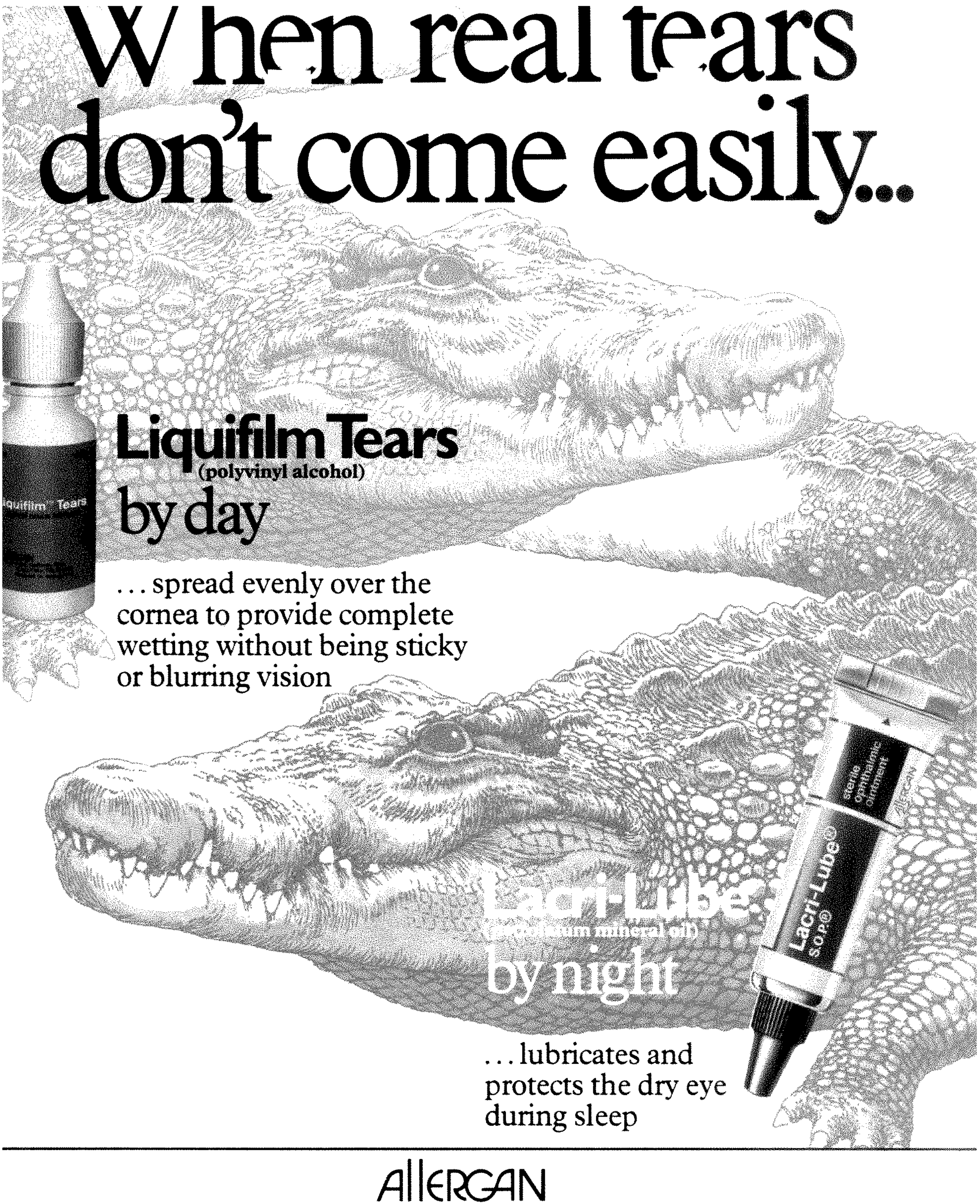

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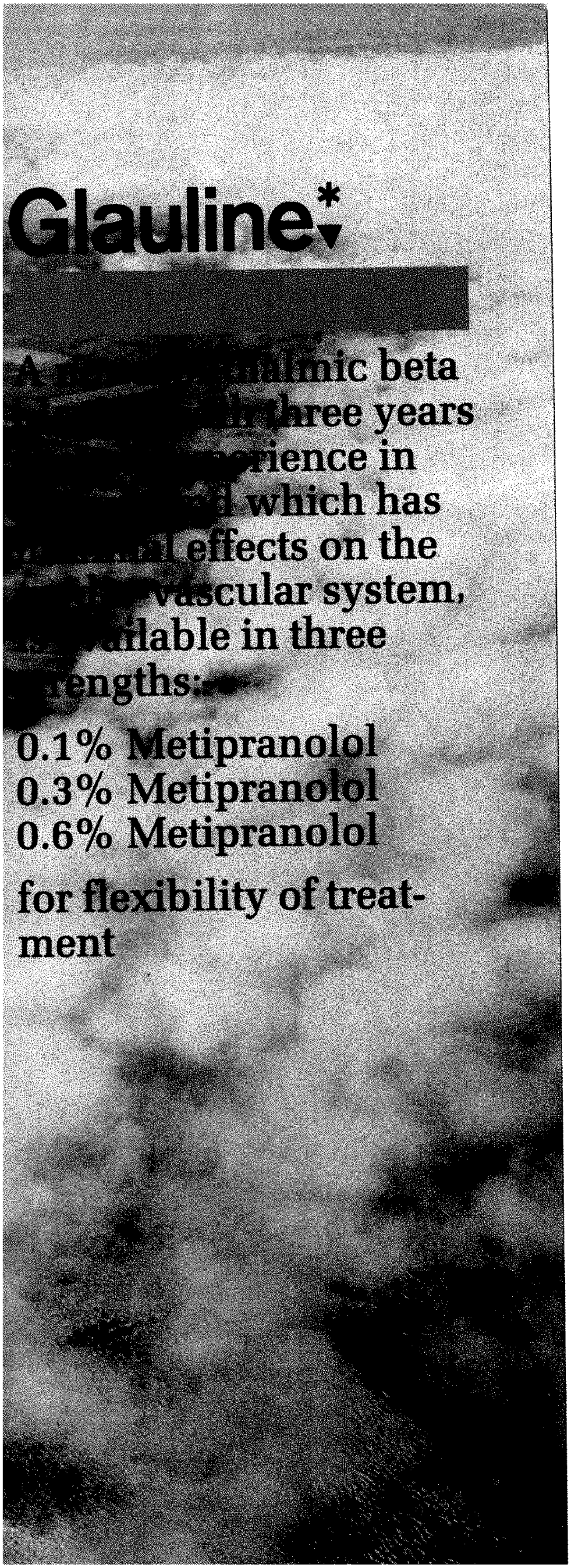

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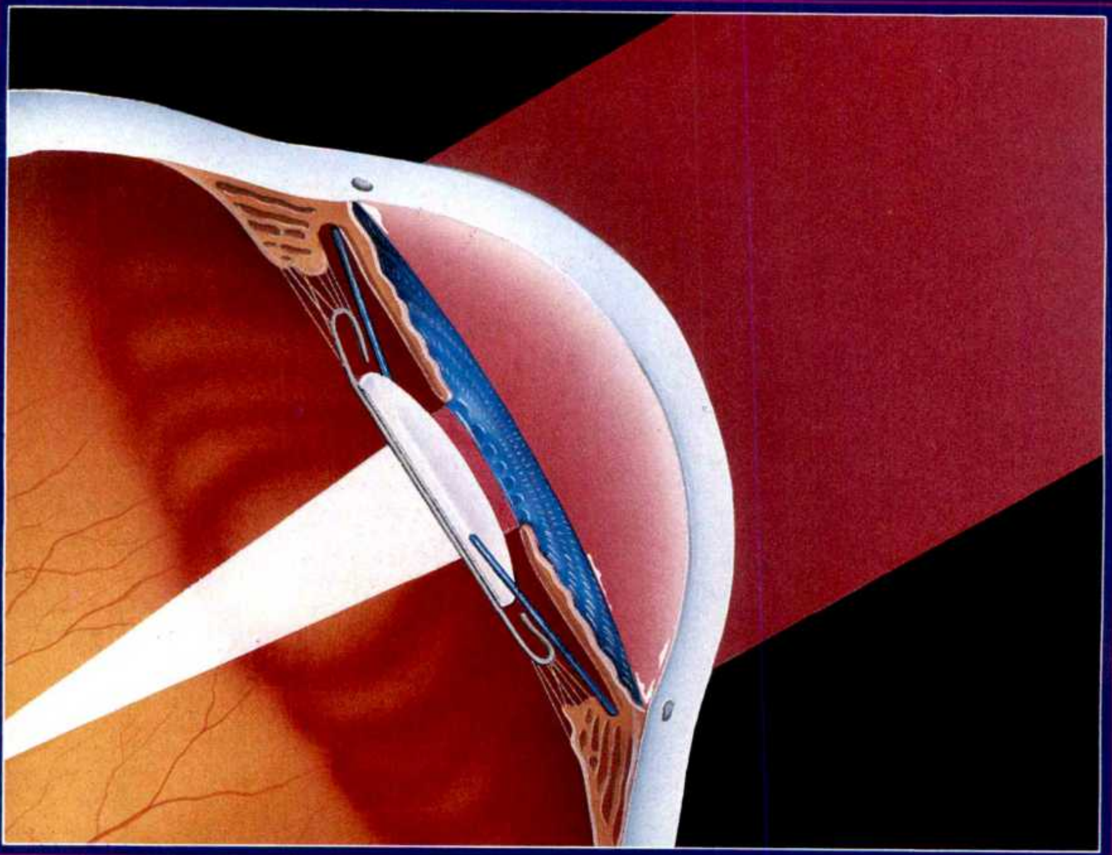

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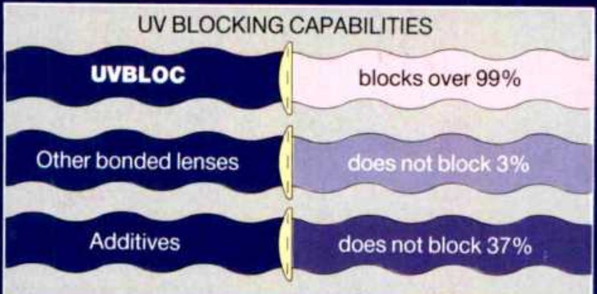

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Anterior chamber depth in open angle glaucoma

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SUMMARY Anterior chamber depth was measured in patients with primary open angle glaucoma, low tension glaucoma, pigmentary dispersion syndrome, and glaucoma suspects. Multiple linear regression analysis demonstrated that anterior chamber depth is a function of sex, age, and refractive error. Values for anterior chamber depth corrected for age and refractive error were greater in patients with pigmentary dispersion syndrome than in patients with other forms of open angle glaucoma or in glaucoma suspects.

The relationships between anterior chamber depth and angle closure glaucoma,[1 2] pseudoexfoliation,[3 4] and pigmentary glaucoma[5] have been investigated. Campbell[6] has suggested that pigmentary dispersion syndrome results from contact between the pigmented epithelium of the iris and the anterior zonular bundles. This theory is consistent with the clinical finding that pigmentary dispersion syndrome occurs with highest frequency in young myopic males, since this group might be expected to have deep anterior chambers resulting in increased contact between the peripheral iris and lens zonule.

We studied the anterior chamber depth (ACD) of patients with primary open angle glaucoma (POAG), low tension glaucoma (LTG), pigmentary dispersion syndrome (PDS), and glaucoma suspects (GS) in order to gain additional information regarding the relationship of ACD to age, sex, refractive error, and diagnosis.

Patients and methods

All patients included in the study underwent complete ophthalmic examination as routinely performed at the Glaucoma Service Diagnostic Laboratory of the Wills Eye Hospital. This included medical and ocular history, visual acuity test, biomicroscopic examination, gonioscopy, funduscopy, stereoscopic colour disc photography, Farnsworth-Munsell 100-hue colour testing, and Octopus computerised perimetry. Intraocular pressure (IOP), pulse, and blood pressure were measured every two hours between 7.30 am and 3.30 pm. Sex, age, and refractive error were recorded for each subject; the spherical equivalent refractive error was calculated for each eye. ACD was measured at the slit-lamp with the Haag-Streit depth measuring attachment No. 2, and was performed by the same examiner on all patients.

Patients were classified as GS on the basis of an optic disc with features suspicious but not diagnostic of glaucoma or consistently raised IOP (>21 mmHg), with normal visual field examination. Patients with POAG had glaucomatous optic nerve cupping and typical glaucomatous visual field loss together with a raised IOP or a history of raised IOP. LTG patients had disc abnormalities and visual field loss typical of this disease,[7 8] with IOP measurements consistently below 21 mmHg. The PDS group displayed a constellation of clinical findings including Krukenberg spindles, mid-peripheral radial transillumination of the iris, and marked pigmentation of the trabecular meshwork; glaucomatous optic disc cupping or visual field loss may or may not have been present.

All eyes treated with miotics were excluded from the study, since these agents are known to shallow the anterior chamber.[9-11] Patients treated with timolol, epinephrine, dipivalyl epinephrine, or oral carbonic anhydrase inhibitors were included in the study.

Statistical evaluation was by single and multiple regression analyses and Student's t test. Data are reported as the mean ± standard error of the mean (SEM). Results were considered statistically significant at $p<0.05$.

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Results

Table 1 contains data for ACD, age, and refractive error for all groups divided by sex. Thirty-eight eyes (67%) with PDS had glaucoma on the basis of glaucomatous optic nerve changes and visual field loss. There were some statistically significant age differences among the groups: females with LTG and PDS were older than their male counterparts (p=0·01 and 0·05, respectively); males with PDS were younger than males with POAG (p=0·003) or LTG (p=0·04); and females with LTG were older than females with POAG (p=0·002). Males with PDS were more myopic than male glaucoma suspects (p=0·001), males with POAG (p=0·004), or males with LTG (p=0·09). Females with PDS were significantly more myopic than females in all other groups (p<0·05).

Mean ACD was significantly greater in males compared with females of each group (GS: p=0·02; POAG: p=0·002; LTG: p=0·05; PDS: p=0·03).

Table 1 *Age, refractive error, and anterior chamber depth*

	Number of patients	*Number of eyes*	*Age (years)*	*Refractive error* (dioptres)*	*Anterior chamber depth (mm)*
Glaucoma suspects:					
male	51	97	50·5±2·1	−0·94±0·23	2·81±0·03
female	62	121	53·9±2·1	−0·57±0·20	2·71±0·03
Primary open angle glaucoma:					
male	46	78	57·0±2·2	−1·38±0·38	2·83±0·04
female	29	56	59·0±2·5	−0·44±0·27	2·65±0·04
Low tension glaucoma:					
male	14	27	54·7±2·7	−2·14±0·46	2·83±0·06
female	41	75	63·6±2·1	0·05±0·27	2·69±0·04
Pigmentary dispersion syndrome:					
male	23	42	46·2±2·8	−3·36±0·55	3·03±0·04
female	9	15	58·0±5·0	−2·02±0·70	2·87±0·07

*Spherical equivalent.

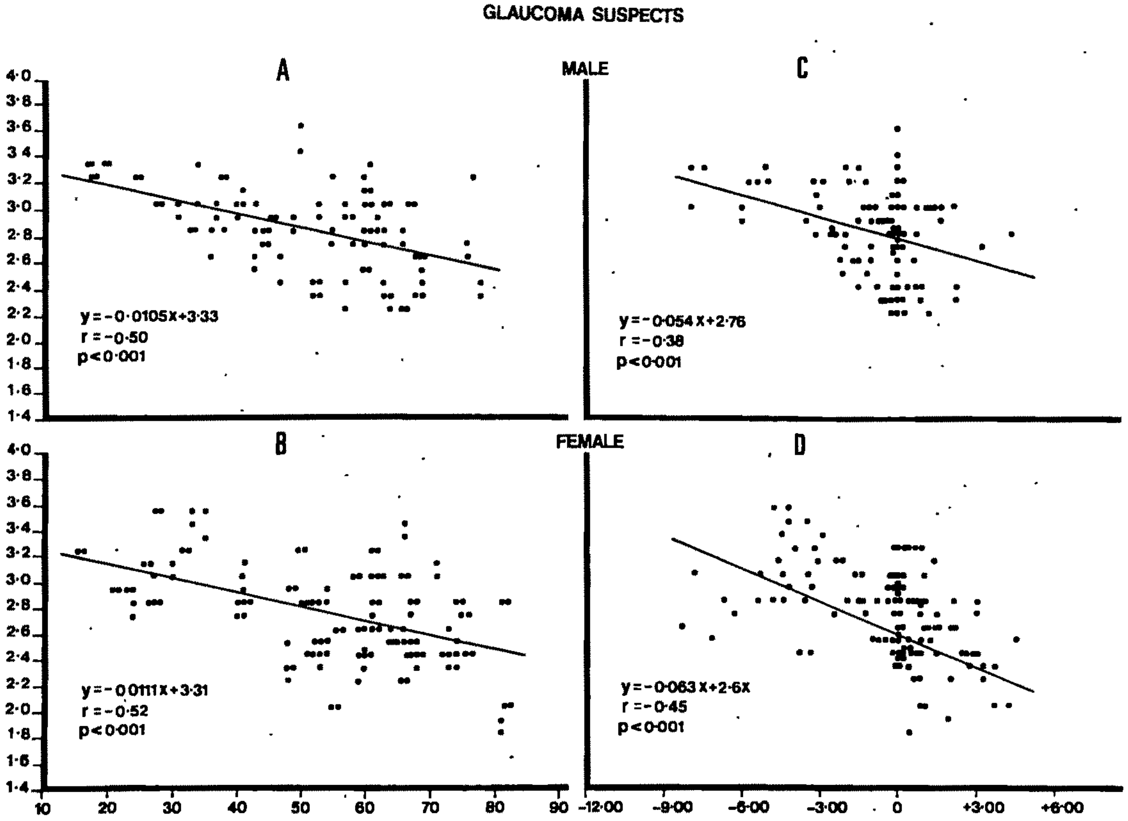

Fig. 1 *Anterior chamber depth (mm) in glaucoma suspects as a function of age (years) in* (A) *males and* (B) *females, and as a function of refractive error (dioptres) in* (C) *males and* (D) *females. The results of linear regression analysis are given along with the correlation coefficient (r) and associated probability (p).*

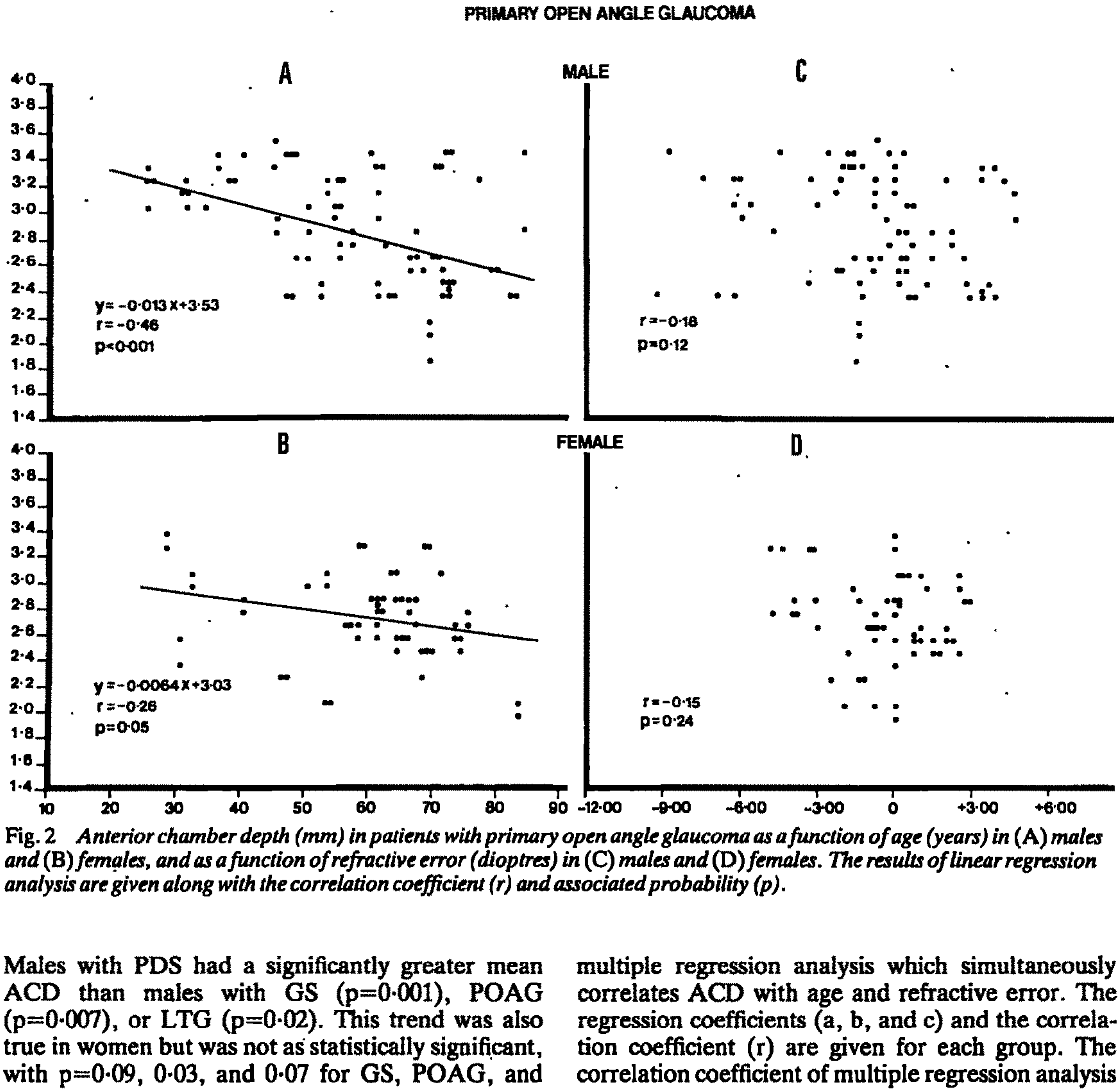

Fig. 2 *Anterior chamber depth (mm) in patients with primary open angle glaucoma as a function of age (years) in* (A) *males and* (B) *females, and as a function of refractive error (dioptres) in* (C) *males and* (D) *females. The results of linear regression analysis are given along with the correlation coefficient (r) and associated probability (p).*

Males with PDS had a significantly greater mean ACD than males with GS (p=0·001), POAG (p=0·007), or LTG (p=0·02). This trend was also true in women but was not as statistically significant, with p=0·09, 0·03, and 0·07 for GS, POAG, and LTG respectively. Such comparisons of mean ACD should be made with caution, however, since significant differences between groups regarding age and refractive error will influence the findings. Accordingly, single and multiple regression analyses were performed to factor out the influences of age and refractive error on ACD.[12]

Fig. 1 through 4 display the measured values of ACD as a function of age and refractive error for males and females of each group. The p value associated with the correlation coefficients are shown on the graphs. There were significant correlations for males and females in most groups between ACD and age, and ACD and refractive error (Figs. 1–4). ACD decreased with increasing age, and increased with increasing myopia. Table 2 contains the results of multiple regression analysis which simultaneously correlates ACD with age and refractive error. The regression coefficients (a, b, and c) and the correlation coefficient (r) are given for each group. The correlation coefficient of multiple regression analysis representing ACD as a function of both age and refractive error was significant for each group (p<0·02). These results allow for the prediction of ACD for a patient of given sex correcting for age and refractive error.

ACD values corrected for age (50 years) and refraction (plano) are given in Table 3. Corrected values for ACD in males and females with PDS were greater than the values for the same sex in all other diagnostic groups. Therefore differences in age and refractive error could not entirely account for the greater ACD found in patients with PDS. There was no significant difference in ACD when eyes with PDS and no visual field loss were compared with eyes with PDS and glaucomatous visual field loss.

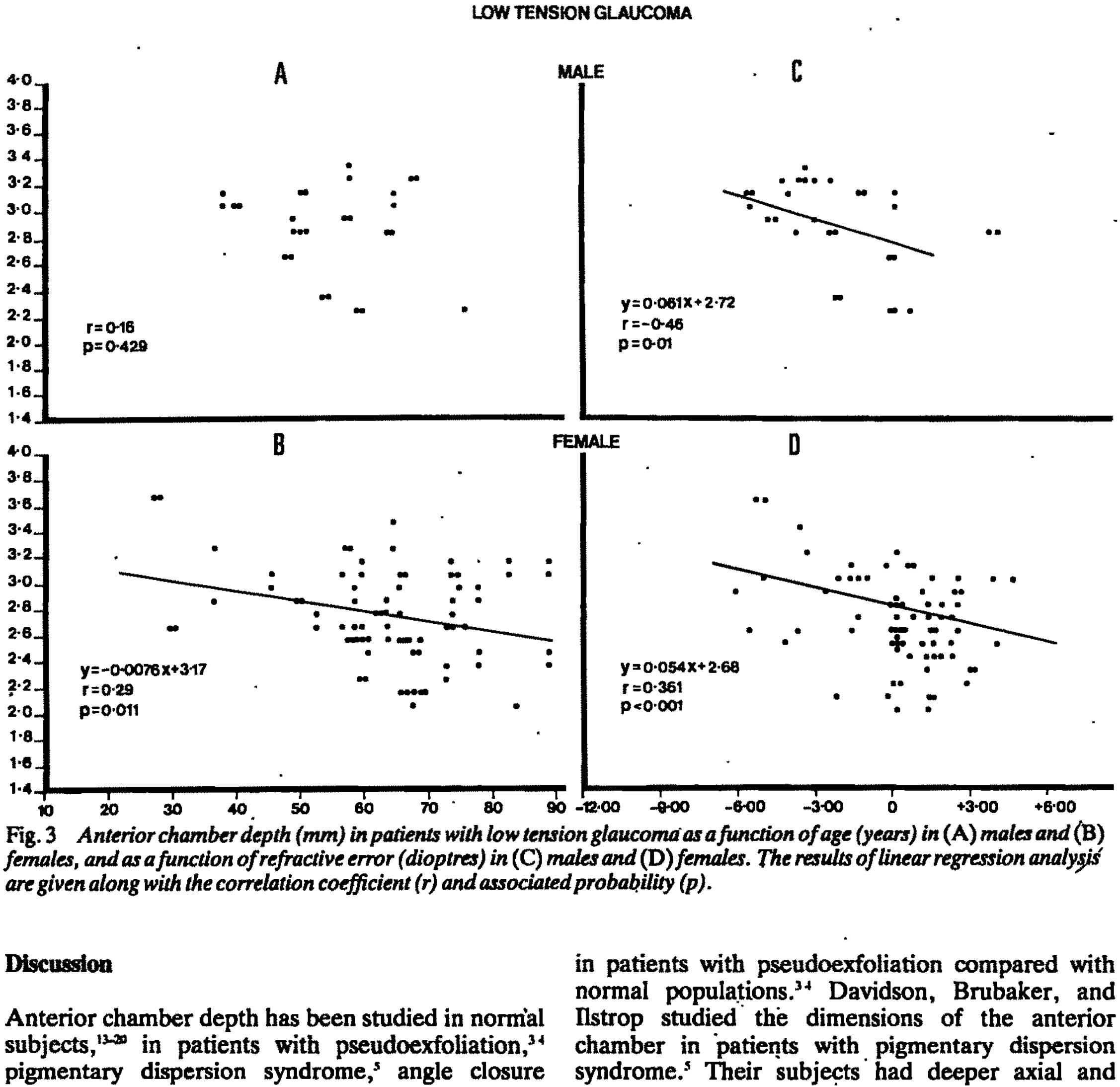

Fig. 3 *Anterior chamber depth (mm) in patients with low tension glaucoma as a function of age (years) in* (A) *males and* (B) *females, and as a function of refractive error (dioptres) in* (C) *males and* (D) *females. The results of linear regression analysis are given along with the correlation coefficient (r) and associated probability (p).*

Discussion

Anterior chamber depth has been studied in normal subjects,[13-20] in patients with pseudoexfoliation,[3,4] pigmentary dispersion syndrome,[5] angle closure glaucoma.[1,2] after retinal surgery,[21,22] and in aphakic eyes.[23,24] Methods have included the use of optical pachymetry,[1-4,10,14,17,19-24] ultrasonic devices,[18] and photogrammetry.[5,8,13] Fontana and Brubaker[13] studied anterior chamber dimensions in normal subjects using a photogrammetric technique. Significant correlations were found with age and refractive error, such that deeper central anterior chambers and greater anterior chamber volume were associated with decreasing age and increasing myopia. Males had deeper anterior chambers than females.

It has been well established that patients with angle closure glaucoma have shallow anterior chambers,[5] and that eyes with a shallow axial ACD are at increased risk for angle closure glaucoma.[1,2,25-27] No significant differences in axial ACD have been found in patients with pseudoexfoliation compared with normal populations.[3,4] Davidson, Brubaker, and Ilstrop studied the dimensions of the anterior chamber in patients with pigmentary dispersion syndrome.[5] Their subjects had deeper axial and midperipheral ACDs than could be accounted for by age, sex, or refractive error. Concavity of the midperipheral iris surface was also demonstrated in this group. These results supported Campbell's mechanical theory of iris pigment dispersion.

We measured ACD in four groups of patients: glaucoma suspects, primary open angle glaucoma, low tension glaucoma, and pigmentary dispersion syndrome (with or without glaucoma). Each group was analysed according to sex, age, and refractive error. The mean ACD in each group was greater in males than in females. Multiple regression analysis revealed significant dependence of ACD on age and/or refractive error for males and females of each group. Age- and refractive-error-corrected values of ACD showed deeper anterior chambers in patients

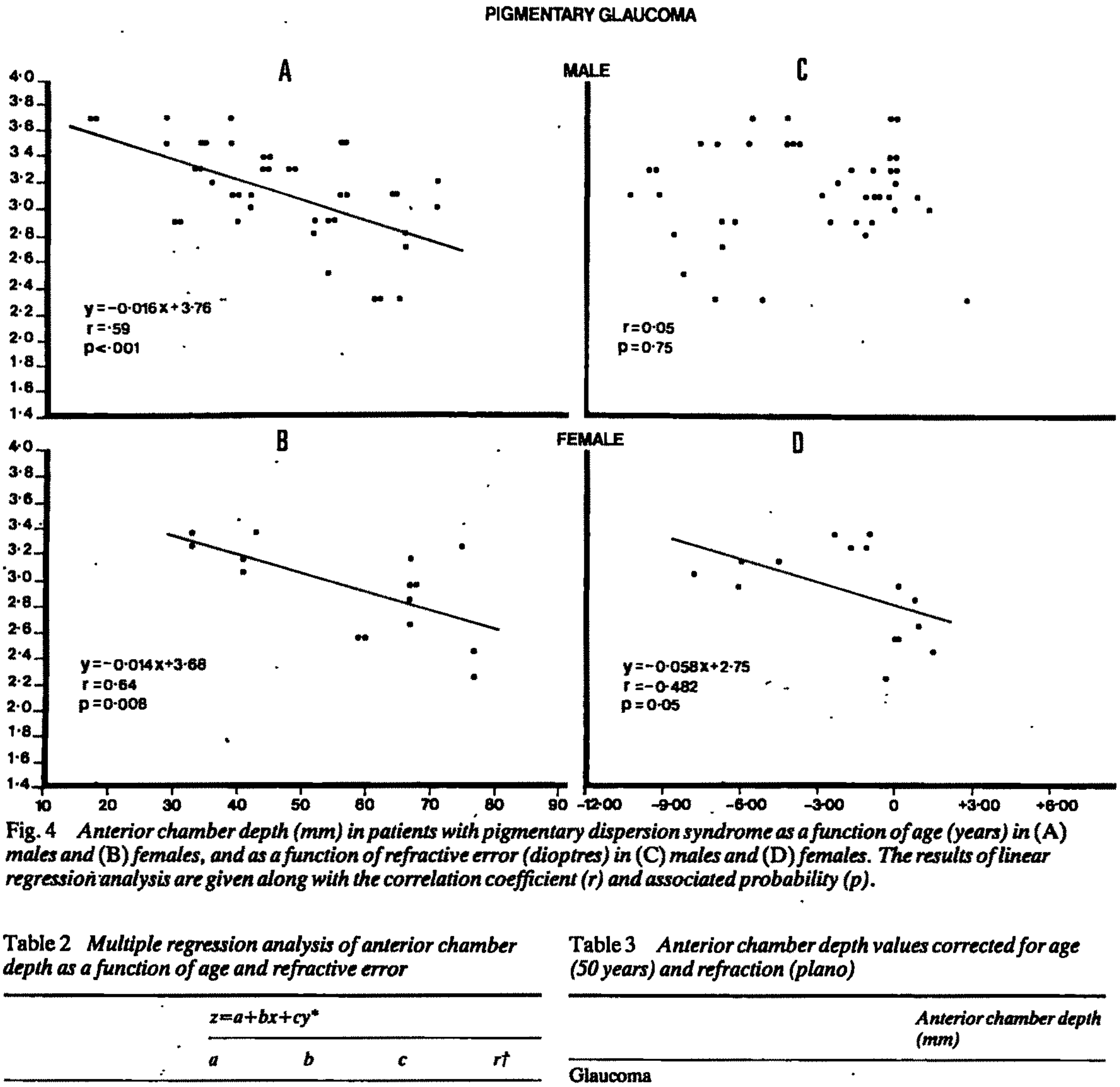

Fig. 4 *Anterior chamber depth (mm) in patients with pigmentary dispersion syndrome as a function of age (years) in* (A) *males and* (B) *females, and as a function of refractive error (dioptres) in* (C) *males and* (D) *females. The results of linear regression analysis are given along with the correlation coefficient (r) and associated probability (p).*

Table 2 *Multiple regression analysis of anterior chamber depth as a function of age and refractive error*

	*z=a+bx+cy**			
	a	*b*	*c*	*r*†
Glaucoma suspects:				
male	3·24	−0·009	−0·020	0·517
female	3·16	−0·009	−0·041	0·588
Primary open angle glaucoma:				
male	3·47	−0·012	−0·018	0·486
female	3·04	−0·007	−0·029	0·314
Low tension glaucoma:				
male	2·99	−0·005	−0·062	0·485
female	2·93	−0·004	−0·044	0·390
Primary dispersion syndrome:				
male	3·76	−0·016	0·001	0·588
female	3·48	−0·012	−0·034	0·686

*For the formula z=a+bx+cy, z=anterior chamber depth, x=age, y=refractive error, and a, b, and c are regression coefficients.
†The values for the correlation coefficient (r) indicates a statistically significant correlation at $p<0·02$ for each group.

Table 3 *Anterior chamber depth values corrected for age (50 years) and refraction (plano)*

	Anterior chamber depth (mm)
Glaucoma suspects:	
male	2·79±0·03
female	2·72±0·03
Primary open angle glaucoma:	
male	2·85±0·04
female	2·70±0·04
Low tension glaucoma:	
male	2·74±0·06
female	2·72±0·04
Pigment dispersion syndrome:	
male	2·97±0·04*
female	2·89±0·07*

*These values for anterior chamber depth are significantly greater ($p<0·05$) than values for the same sex in other diagnostic categories.

with pigmentary dispersion syndrome than in the other diagnostic categories. Corrected values for ACD were greater for males within each group. No significant differences in ACD corrected for age and refractive error were found between groups of patients of the same sex with primary open angle glaucoma, low tension glaucoma, or glaucoma suspects.

These results indicate that patients with pigmentary dispersion syndrome have deeper anterior chambers than can be accounted for by age, sex, or refractive error. Our findings corroborate those of Davidson *et al.*[5] and lend support to Campbell's theory[6] of pigmentary erosion secondary to iris-zonular contact.

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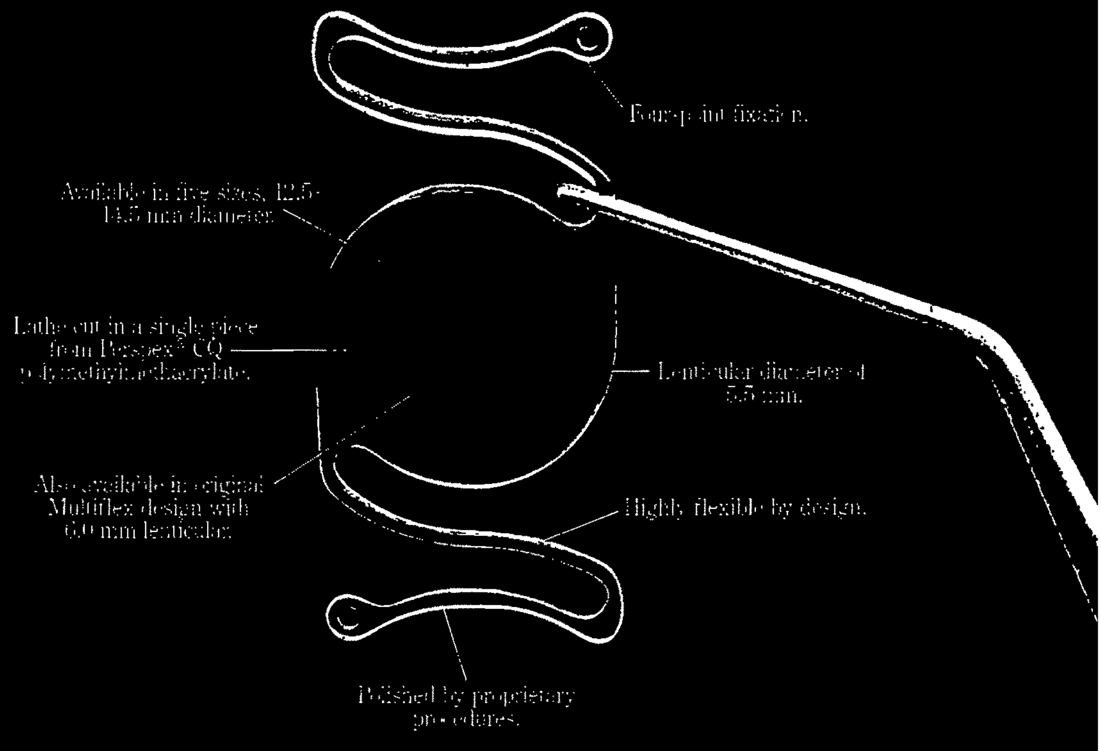
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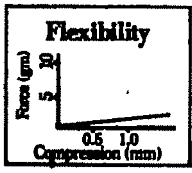

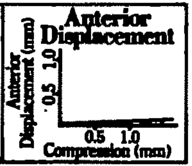

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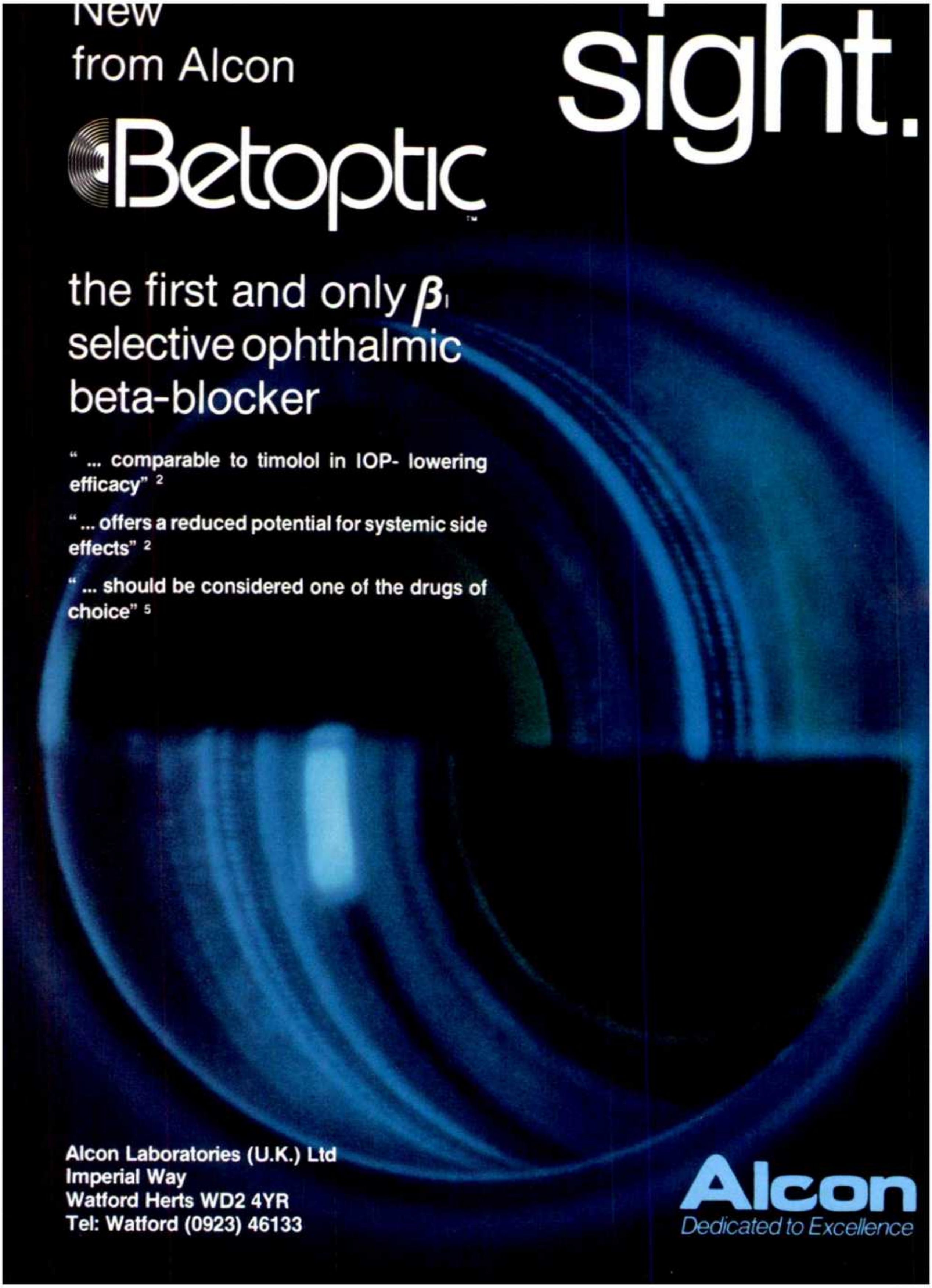

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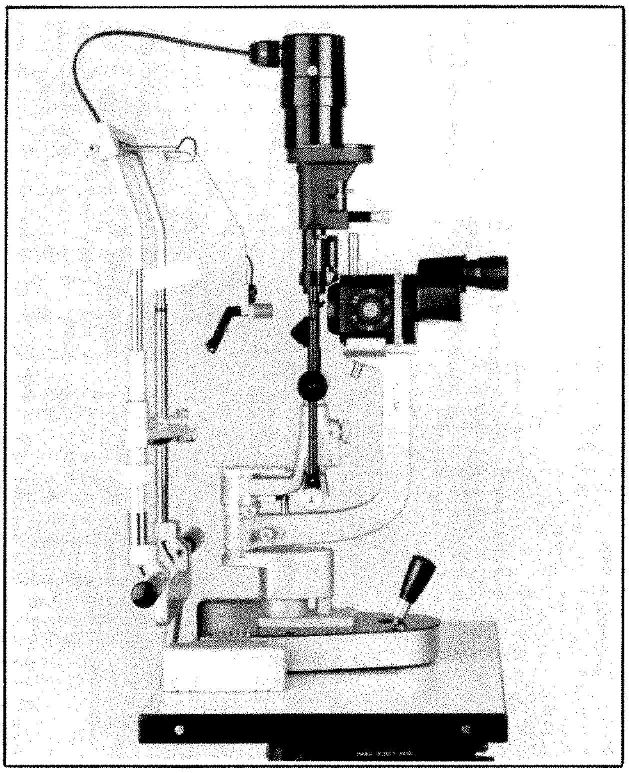

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Response of exfoliation glaucoma to laser trabeculoplasty

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SUMMARY The comparative response of exfoliation (EF) glaucoma and primary open-angle glaucoma (POAG) to laser trabeculoplasty (LTP) was studied retrospectively. The effectiveness of argon laser trabeculoplasty (LTP) was compared in 26 eyes of patients with EF glaucoma (uncontrollable by maximally tolerated medical therapy) and 28 eyes of patients with POAG (controls). 64% of the POAG group and 46% of the EF glaucoma group received treatment of the entire angle in two divided sessions in order to reduce the intraocular pressure (IOP) to ≤22 mmHg. All second treatments were performed at least four to six weeks after the initial session. Evaluation of the postoperative course of IOP by means of the Kaplan-Meier curve for data analysis indicated that EF patients 'failed' at a faster rate than POAG patients after both the initial and consecutive laser treatments. The rate of failure in the EF group, however, was greater following the initial 180° treatment. Although patients with EF glaucoma have a large initial reduction in intraocular pressure after LTP, to increase the probability of maintaining intraocular pressures of ≤22 mmHg consecutive 180° treatments should be considered.

Laser trabeculoplasty (LTP) has proved effective in lowering the intraocular pressure (IOP) of patients with primary open-angle (POAG) and other secondary glaucomas. Patients with exfoliation glaucoma (EF), for example, have a significant reduction in intraocular pressure after laser treatment. Ritch and Podos, summarising the results from eight series of EF patients (n=111), reported that 94 had reduced intraocular pressures after LTP, obviating the need for filtration surgery.[1] Moreover, their data suggested that LTP was more successful in treating patients with EF than with POAG. In the series reported by Thomas *et al.*[2] laser therapy was successful in 97·1% of patients with EF glaucoma versus 85·2% with POAG. Zborowski *et al.* noted a similar trend, but the difference was not statistically significant.[3] The rate of failure reported after LTP is also low for EF patients. Of the 34 patients in the series of Thomas *et al.*[2] only one failed. Ritch and Podos[1] found only four treatment failures in a series of 15 EF patients, which had a range of follow-up of three months to two years.

Thus, it would appear that LTP is effective in treating patients with EF glaucoma. The difference between EF and POAG with respect to rate of failure after LTP has not been addressed. A retrospective investigation was undertaken to examine this issue.

Patients and methods

All data were taken from the files and records of the Glaucoma Consultation Service of the Massachusetts Eye and Ear Infirmary. The effectiveness of LTP was examined in 26 eyes of patients with EF who had progressive optic disc and visual field deterioration with poor IOP control despite maximally tolerated medical therapy. The eyes in the experimental group were compared with 28 lasered eyes randomly selected from the POAG population of the Glaucoma Consultation Service. EF glaucomatous eyes were characterised clinically by (*a*) the presence of 'flakes' on the anterior capsule of the lens, and (*b*) perimarginal pupillary atrophy associated with open-angle glaucoma. The POAG patients also qualified as candidates for LTP on the basis of field and disc progression while on maximally tolerated medical therapy. The controls were matched with the

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experimental group according to the date of the laser treatments and age. Cases with a history of previous ocular surgery, trauma, or uveitis were excluded. All patients were phakic and over 55 years of age.

All patients had been treated with an argon laser (Coherent Model 900) by the technique of Wise and Witter.[4] The average laser energy was 5·5 joules for the EF group. The average number of shots in the eyes per 180° of treatment was 48 (SD8) for the POAG eyes and 53 (SD11) for the EF eyes ($p<0{\cdot}05$) The power range was 700–1250 mW, and the duration was always 0·1 s. All patients continued their antiglaucoma medications preoperatively and were placed on topical steroids for five days after laser therapy. Some eyes were treated in two sessions (180° each session). However, if the initial session resulted in reduced intraocular pressures such that the patient's glaucoma was no longer progressive, the remaining 180° of the angle was left untreated.

A failure was defined as any eye with intraocular pressure greater than 22 mmHg one month or more after LTP, or any eye requiring filtering surgery. Eyes requiring second laser treatments were not necessarily considered failures.

Kaplan-Meier survival curves[5] were used to analyse the time course of failure in the various subgroups. Student's *t* test was used to compare follow-up IOP data with baseline data. Independent sample *t* tests were used to compare the EF and POAG groups.

The mean age was 70 (SD11) years in the POAG group versus 75 (SD7) years in the EF group ($p<0{\cdot}05$). The mean age of patients was 72 (SD7) years for those with unilateral EF ($p<0{\cdot}01$). Twelve eyes were studied from patients with unilateral EF and 14 eyes from patients with bilateral EF.

The mean preoperative IOP in the POAG group was 22·4 (SD3·8) mmHg versus 25·5 (SD7·8) mmHg in the EF group ($p<0{\cdot}08$). The average postoperative pressure after the initial laser treatment at four to six weeks was 17·3 (SD4·5) mmHg for the controls versus 19·1 (SD6·0) mmHg for the EF glaucoma group. The mean IOP seven to eight weeks after the first laser treatment in the control group was 16·5 (SD4·8) mmHg and 15·8 (SD7·9) mmHg in the EF group.

A greater reduction in IOP was observed in the EF glaucoma group compared with the POAG group after the initial 180° laser treatment ($p<0{\cdot}10$). At seven to eight weeks after LTP the difference was −5·6 (SD4·8) mmHg in the EF group.

The difference between groups after the second laser treatment was not as marked. The mean IOP prior to the second laser treatment was 18·9 (SD2·7) mmHg for the control group and 23·4 (SD9·7) mmHg for the EF group. At four to six weeks after the second laser treatment the mean IOP for the control group was 16·1 (SD2·1) mmHg and 18·5 (SD3·9) mmHg for the EF group.

Table 1 *Pressure reduction after initial laser treatment: cumulative probability of maintaining intraocular pressure* $\leq$*22 mmHg*

Follow-up time (weeks)	*POAG (%)*	*Exfoliation glaucoma (%)*		
		All	*Unilateral*	*Bilateral*
4–6	88	74	64	92
7–8	83	74	64	92
12	77	74	64	92
33	77	59	51	73
59	64	59	*	*

*Data are presented only for categories where the denominator was at least 5.

Percentage of 'successful' patients remaining in the POAG, unilateral EF, and bilateral EF groups at increasing periods of follow-up after treatment of the initial 180° of angle. Data were analysed by Kaplan-Meier survival curves.

The relative failure rates were assessed by the Kaplan-Meier curve. The data were analysed in two groups: (1) IOP after treatment of the initial 180° (Table 1), and (2) IOP after treatment of the second 180° (Table 2). After the first treatment a greater percentage of patients failed to achieve acceptable pressures in both the unilateral and bilateral EF glaucoma groups than in the POAG group. After the second laser treatment more patients in the unilateral EF glaucoma group failed than in the POAG group. The sample with bilateral EF glaucoma was too small to analyse.

Mild transient uveitis occurred in all patients after LTP and was successfully treated with topical steroids. No irreversible complications, such as corneal burns or permanent PAS peripheral anterior synechiae, were noted. Four controls and one unilateral EF patient required filtration surgery at 12, 43, 47, 77, and 47 weeks respectively.

Table 2 *Pressure reduction after final laser treatment: cumulative probability of maintaining intraocular pressure* $\leq$*22 mmHg*

Follow-up time (weeks)	*POAG (%)*	*Exfoliation glaucoma (%)*	
		All	*Unilateral*
4–6	100	91	83
7–8	88	71	67
33	59	*	*
59	59	*	*

*Data are presented only for categories where the denominator was at least 5.

Percentage of 'successful' patients remaining in the POAG and unilateral EF, at increasing periods of follow-up after treatment of the consecutive 180° of angle. Data were analysed by Kaplan-Meier survival curves.

Discussion

The results of this investigation suggest a greater failure rate for eyes with EF glaucoma than in a group of POAG controls. It is possible that these failures may be unrelated to loss of efficacy of LTP; rather they may be a reflection of the natural course of EF glaucoma. Alternatively, the fact that more POAG patients in this series underwent treatment of the full 360° of the trabecular meshwork may also have affected the outcome. It has been suggested that treatment of the entire angle is necessary to maintain a reduction of IOP.[6] Our findings suggest that the trabecular meshwork of patients with EF glaucoma should be treated for the full 360°, despite the ability to achieve pressures ≤ 22 mmHg and even when the optic disc or visual field do not deteriorate further. The benefits of 360° treatment, however, must also be weighed against the possible risk of increasing the intraocular pressure. Thomas *et al.*,[2] for example, observed a risk of worsening the glaucoma status after trabeculoplasty.

The current series also suggests that EF patients with unilateral disease respond less well to laser therapy than EF patients with bilateral disease. Three postulates are the following: (1) The trabecular meshwork of patients with unilateral EF glaucoma may be more resistant to the effects of laser. (2) Physicians treating patients with unilateral EF tend to wait longer before performing LTP because the patient is less impaired. (3) Because the bilateral EF patients in this series were older (78 (SD7) years bilateral EF versus 72 (SD7) years unilateral EF), the success of LTP may have been enhanced. Richardson and Epstein have shown trabecular beams in EF glaucoma to be intact, unlike the denuded, collapsed beams of pigmentary glaucoma.[7] Although morphological differences have been noted between EF glaucoma and other glaucomas, there is no evidence so far of differences between unilateral and bilateral EF. Further histological studies would be necessary to determine whether any morphological or biochemical differences exist between eyes with unilateral versus bilateral EF.

The EF cases in this series had a greater reduction of IOP than the POAG controls. This finding agrees with the series of patients reported on by Thomas *et al.*[2] On the other hand a higher preoperative IOP (25·5 (SD7·8) mmHg for EF versus 22·4 (SD3·8) mmHg for POAG) predicts a greater change in pressure after laser treatment. Another explanation may be related to the greater degree of pigmentation found in angles with EF. It is possible, for instance, that the thermal effect of laser treatment is more effectively absorbed in angles containing greater amounts of melanin.

The high percentage of 'failure' in the EF group may be attributed to the very narrow definition of failure in this study. Our criteria did not account for fluctuations in IOP as a function of time. Perhaps intraocular pressures greater than 22 mmHg measured in two consecutive visits would have been a better criterion. Nevertheless the same criteria were applied to both groups.

The results of this study clearly point to the need for a prospective investigation on a larger series of patients and standardisation of treatment. Although patients with EF appear to fail at a faster rate than patients with POAG, LTP remains an important adjunct to the management of EF glaucoma. Patients who maintain pressures in the high teens after 180° laser treatments should be considered for consecutive treatments in order to ensure maintenance of reduced intraocular pressure, and patients should be closely monitored for any deterioration of visual field and optic disc after laser therapy to evaluate the need for filtration surgery.

We thank Ms Ellen Hertzmark for her assistance with statistical analysis.

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Augmented medial rectus recession in the management of esotropia

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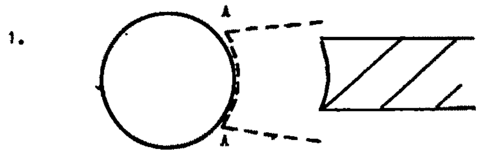
SUMMARY Forty-six children awaiting surgery for concomitant esotropia were placed into two matched groups. One group received bilateral medial rectus recessions, while the second group received augmented bilateral medial rectus recessions. By recessing the conjunctiva and subconjunctival tissue in addition to the medial rectus we consistently increased the correction obtained. With bilateral medial rectus recession to correct large angle esotropia application of the augmented technique is more likely to provide a full correction.

In the surgical management of concomitant esotropia there are a number of potential advantages in the use of symmetrical medial rectus recessions rather than recession and resection of both horizontal recti of one eye. These include preservation of all muscle tissue, a reduced incidence of postoperative granuloma formation,[1] and a reduced tendency to induce astigmatism in the early postoperative period.[2] However, for the surgeon wishing to employ symmetrical recessions of the medial recti there is concern that medial rectus recessions alone may be inadequate fully to correct large angle esotropia. We therefore considered it worthwhile to explore the possibility of augmenting the effect of bilateral medial rectus recessions in large angle esotropia by simultaneously recessing the overlying conjunctiva and anterior Tenon's capsule.

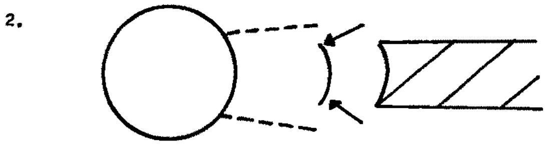
Patients and methods

Two groups of children receiving surgery for large angle concomitant esotropia were compared. The groups were matched for sex, age at the time of surgery, type of convergent deviation, preoperative angle of deviation, refractive error, degree of amblyopia, and the potential for binocular single vision as assessed at the preoperative examination by tests appropriate for age.

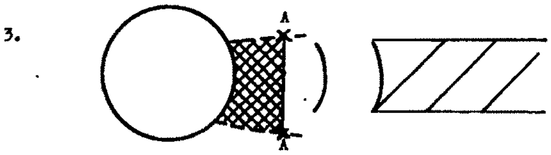
One group of children then received bilateral medial rectus recessions with full reapposition of the conjunctiva, while the second group received (in addition to their muscle recessions) recession of the conjunctiva and Tenon's capsule to a maximum of 5 mm from the limbus, or to a point immediately in front of the original muscle insertion if this was less than 5 mm (Fig. 1).



Limbal Peritomy with radial relieving incisions.



Muscle recession.
Arrows indicate original muscle insertion.



Conjunctiva recessed to a point anterior to original muscle insertion.

▨ Bare sclera

Fig. 1 *Technique of conjunctival recession.*

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Table 1 *Comparison of patients receiving conventional bimedial recessions (group 1) with those receiving augmented bimedial recessions (group 2)*

	Group 1	*Group 2*
Mean age at surgery	39·5 (months)	39·8 (months)
Mean preop. deviation	41·5 (prism dioptres)	48·9
M:F	13:10	13:10
No amblyopia: amblyopia	21:2	20:3
Potential BSV	4	4
Emmetropia	14	13
Hypermetropia >2·00 DS	4	4
Astigmatism >1·00 DC	3	3
Unilateral:alternating	16:7	8:15
Congenital:non-congenital	11:12	10:13

The surgery was carried out by one of us (HEW) or under his direct supervision, and was by our standard technique of muscle exposure, a limbal conjunctival incision, with two radial relieving incisions. The muscles were secured to the globe by a 6/0 gauge coated polyglactin suture, and the limbal conjunctival incision was closed with four interrupted 8/0 virgin silk sutures when full reapposition was employed, and either two or four interrupted virgin silk sutures when the conjunctiva was recessed. The reduction in the angle of deviation was then assessed two weeks, six weeks, and six months after surgery, and the prism dioptres of correction per millimetre of muscle recession were compared in the two groups.

Results

Each group contained 23 children, and their details are shown in Table 1. Except for the number of children showing free alternation preoperatively, statistical analysis revealed no significant differences between the two groups.

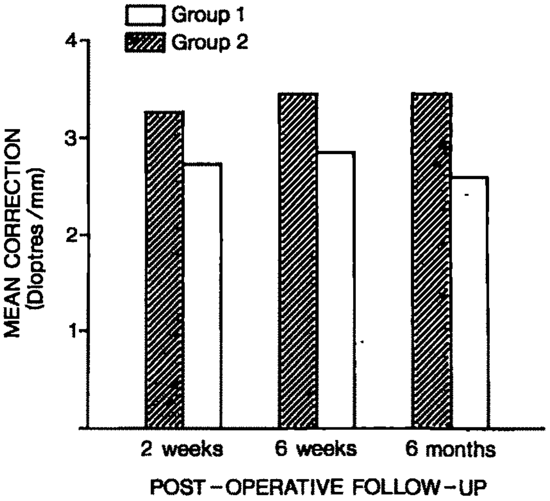

Fig. 2 *Comparison of the mean correction achieved (prism dioptres per mm recession) at 2 weeks, 6 weeks, and 6 months for the two groups.*

The mean correction in prism dioptres per millimetre of muscle recession was calculated for the two groups at the three follow-up intervals (Fig. 2). Detailed examination of the two groups showed that the factors which had greatest influence on the amount of correction achieved were the age of the patient at the time of surgery and the size of the preoperative deviation. The two groups were therefore further analysed to determine the correction achieved two weeks, six weeks, and six months postoperatively for children of different ages (Fig. 3), and with different preoperative angles of deviation (Fig. 4) by the two surgical approaches. With either factor it was again found that the augmented recession produced a greater effect.

No difference was found in the response to surgery of either type between those children considered to have the potential for binocular single vision and those considered to have constant suppression. Similarly no difference in response to surgery was found between children with different refractive errors or differing durations of strabismus prior to their surgery—though all these factors are being examined in a much larger series.

Discussion

Such is the variability of individual response to extraocular muscle surgery that comparisons of the

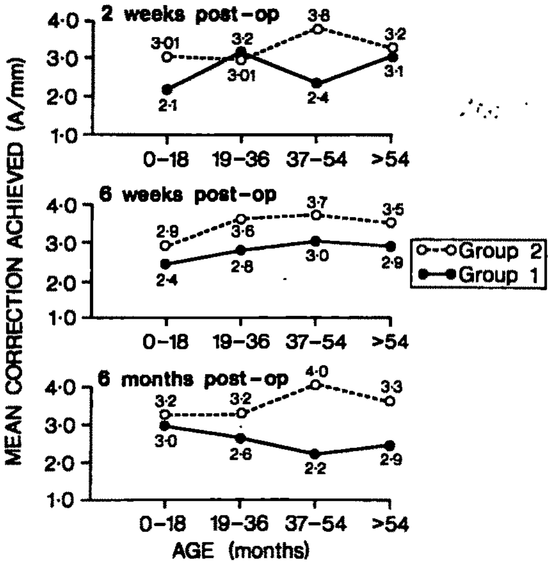

Fig. 3 *Comparison of the mean correction achieved with each technique in children of different ages at the time of surgery.*

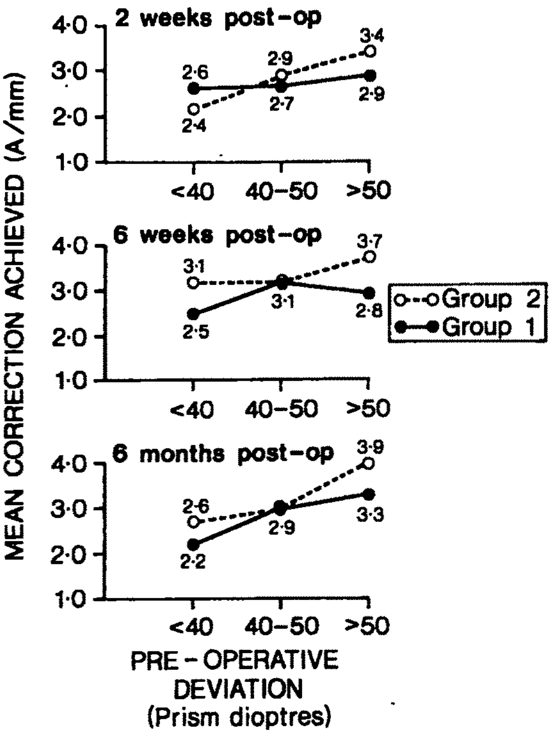

Fig. 4 *Comparison of the mean correction achieved with each technique, in children with different preoperative angles of deviation.*

response to different surgical procedures are difficult to analyse statistically. None the less, all the comparisons we have used demonstrate an augmentation of the effectivity of bilateral medial rectus recession when it is combined with a conjunctival recession.

The importance of changes in conjunctiva and Tenon's capsule in contributing to the mechanical components of strabismus in thyroid eye disease has long been recognised.[3] Similarly, many authorities have emphasised the need for repeated force duction testing during the correction of cicatricial strabismus, recognising that multiple tissue components contribute to the overall effect.[4] However, relatively little has been written on the influence of non-muscular elements in determining the size of an uncomplicated concomitant strabismus. Since we have been able to demonstrate an increased effect with this augmented surgery (confirming the report of Helveston *et al.*[5]) it must be assumed that in a long-standing deviation, even with a full range of ocular movements, secondary changes occur in conjunctiva and Tenon's capsule which tend to increase the underlying angle of squint. This being so, it is perhaps surprising that no increased augmentation is found in children with longer durations of squint prior to surgery. However, no children in this series were operated on less than six months after the onset of their strabismus. One would also expect that in the large angle congenital esotropia with habitual limitation of abduction the changes in conjunctiva and Tenon's capsule would be greater, and thus the influence of non-muscular recession also greater. This proved to be the case, with a mean increase in effect of 0·87 dioptre per mm of muscle recession (a 30·9% increase) achieved six weeks postoperatively in those squints measuring 50 dioptres or more preoperatively.

Recent reports[6 7] have advocated the use of supramaximal recession of the medial recti for large angle deviations and have reported no postoperative convergence weakness. We routinely employ 6 mm recessions for large angle esotropias and, with the added effect from augmented recession, have only rarely been troubled by significant residual esotropia. For this reason we have not yet resorted to the larger recessions which are apparently possible.

The even greater augmentation achieved by Helveston *et al.*[5] with this technique is difficult to explain but may relate to differences in technique, and in particular the extent of the peritomy used to approach the muscle and therefore the volume of conjunctiva released.

Certain differences in the behaviour of eyes receiving this bare sclera closure have been noted but not analysed in detail. Firstly, the eyes tend to be 'whiter' in the immediate postoperative period. Secondly, it has been our impression that postoperative discomfort may be a little more prolonged (by one or two days), as is commonly experienced when using a bare sclera closure after adjustable suture surgery.[8] Finally, caution must be exercised in covering the site of the original medial rectus insertion with conjunctiva, since failure to do so may result in unacceptable cosmesis.

CONCLUSION

In large angle esotropia (greater than 40 prism dioptres) the surgeon employing bilateral medial rectus recession as his primary procedure may wish to enhance the effect of conventional surgery rather than employ supramaximal recessions (of 7 or 8 mm). In this case combining the muscle recession with recession of the overlying conjunctiva and Tenon's capsule is an effective and simple measure.

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Results after β-irradiation (^{106}Ru/^{106}Rh) of choroidal melanomas: 20 years' experience

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SUMMARY From 1964 to 1984 309 patients with choroidal melanoma were treated with ^{106}Ru/^{106}Rh β ray applicators (1000 Gy at the apex of the tumour within 7–14 days). In 216 cases (69·9%) this treatment was successful for a mean follow-up period of 6·7 years after irradiation. In 53 cases (17·2%) the eye had to be enucleated, and 40 patients (12·9%) died from metastases within this period. Of the 216 successfully treated patients 114 (52·8%) developed flat scars and 49 (22·7%) retained a visual acuity of 1·5–0·5. Radiogenic late complications with damage to the retinal capillary system were the main causes of visual deterioration, especially in eyes with tumours close to the posterior pole. The survival rate is substantially higher than that for patients whose eyes were primarily enucleated. β Ray applicators with ^{106}Ru/^{106}Rh can be recommended as an effective tool and a simple and cheap procedure to cure patients with small and medium sized choroidal melanomas. They save the eye without endangering our patients' lives.

Stallard[1] was the first ophthalmologist who treated patients successfully with ^{60}Co plaques and proved that the earlier assumption of absolute radioresistance of choroidal melanomas could not be maintained. After β irradiation of conjunctival melanomas had yielded satisfactory results,[2] and to reduce the severe radiogenic side effects using ^{60}Co, we tested other radionuclides, and ^{106}Ru/^{106}Rh was found to be a suitable energy source for treating intraocular tumours.

Freundlich[3] had described in 1949 the radionuclide ^{106}Ru/^{106}Rh for high-dosage local irradiation. The decay of ^{106}Ru via ^{106}Rh to the stable element ^{106}Pa produces β rays having an energy of 3·54 meV (79%), 3·0 meV (8%), 2·4 meV (11%), and 2·0 meV (2%), so that the depth of penetration into the tissue is greater than by ^{90}Sr/^{90}Y.

As shown in previous studies, ^{106}Ru/^{106}Rh applicators make it possible to deliver high doses to the tumour without danger of radiogenic damage to the healthy parts of the eye and with a minimum lens exposure.[4-6]

Material and methods

We used concave mirror-like applicators consisting of pure sheet silver of 1·0 mm thickness which contain ^{106}Ru/^{106}Rh. The shell-shaped applicators have a spherical radius of 12–14 mm. They contain the radioactive material as a thin film of the insoluble ^{106}Ruthenium evenly distributed. The fused front window of the applicator on the concave side is 0·1 mm and the back 0·9 mm thick, and it absorbs nearly 95% of the 3·5 meV β radiation; this is important in practice. The surface dose rate is about 120 mGy per minute, making it possible to apply a dose of 1000 Gy (100 000 rad) at the base of the tumour and 100 Gy (10 000 rad) at its apex in about six days.

^{106}Ru/^{106}Rh ophthalmic applicators have two ears by means of which they can be sutured to the sclera. Five types of ^{106}Ru applicators (CCA, CCB, CCC, COB, and COC) are available. For the treatment of tumours in the vicinity of the optic nerve the types COB and COC have a sector cut out specifically for the nerve*.

The surface dose rate for each applicator is measured with a special scintillation probe, which is calibrated by means of a so-called extrapolation chamber. To check the equal distribution of radioactivity the surface dose rate is measured in 9–17

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*Obtainable from Isocommerz GmbH, DDR-1115 Berlin, Lindenberger Weg, German Democratic Republic.

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Table 1 *Types of applicator*

Source type	*External diameter (mm)*	*Inactive edge (mm)*	*Spherical radius (mm)*	*Nominal activity (MBq)*	*Nominal activity (mCi)*
CCA	15	0·5	12	15	0·4
CCB	20	0·5	12	18·5	0·5
CCC	25	0·5	14 (on request: 13)	26	0·7
COB	20	0·7	12	18·5	0·5
COC	25	0·7	14 (on request: 13)	22	0·6

For all types the approximate surface dose rate is 120 MgY/min (12 rad/min) ± 30%.

different positions of the surface in water. The results refer to the activity at the centre of the applicator.

Between January 1964 and December 1984 309 patients (168 male, 141 female) suffering from choroidal melanoma were treated with ^{106}Ru/^{106}Rh β-applicators. The average age was 52·25 years. The tumour destructive dose—following Stallard's recommendation—was at least 100 Gy at the apex of the tumour. Thus values above 1000 Gy may be reached at the tumour base. An irradiation period of 8 to 14 days seemed to be the optimum exposure time.

The conjunctiva, Tenon's capsule, and, if necessary, muscles were incised under local or, better, general anaesthesia so that the applicator could be placed on the sclera as closely as possible to the tumour base, which had to be carefully localised by transillumination or diathermy. Details of the surgical procedure have been published.[4 5]

Tumour regression was recorded on follow-up examinations by fundus photography, ultrasonography, and fluorescein angiography. The average follow-up period was 6·7 years. One hundred and eighty-eight patients were followed-up for more than five years (average 9·4 years) and 87 were observed for more than 10 years after irradiation.

To describe the extent of the primary tumour the pretreatment clinical classification, designated TNM, was used as recommended by the International Union against Cancer (UICC).[7]

Results

Out of 309 treated patients 190 (61·5%) are alive and have both eyes intact, in 44 (14·2%) the eye had to be enucleated, and 75 patients (24·3%) died—40 from metastases and 35 from other or unknown causes (Fig. 1).

In this study those patients whose tumours had either changed to a flat scar or had shrunk to a still appreciable greyish or black mass with scarring of the tissue around the tumour, which had remained unchanged for more than one year, were considered to have been treated successfully. Moreover those patients who died later from other causes than metastases and whose choroidal melanoma had shrunk or cicatrised were also included as successfully treated cases. Only those patients who died from metastases or whose eyes had to be enucleated were counted as failures.

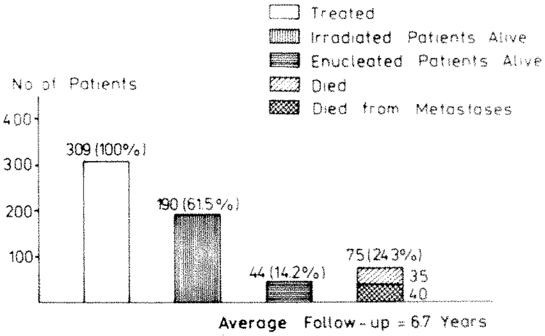


Fig. 1 *Results after β irradiation with ^{106}Ru/^{106}Rh plaques of 309 patients.*

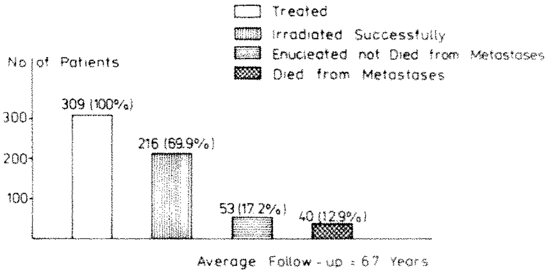


Fig. 2 *Results after β irradiation with ^{106}Ru/^{106}Rh plaques of 309 patients.*

Thus 216 patients (69·9%) out of 309 were treated successfully and have been under observation for a mean period of 6·7 years after irradiation (shortest period one year, longest 21 years). Fifty-three (17·2%) patients' eyes had to be enucleated because of tumour new growth but they have not died from metastases. Forty patients (12·9%) died from proved metastases in this period of 20 years (Fig. 2).

One hundred and eighty-eight patients could be followed up for more than five years (101 patients for 5–9 years, 63 patients for 10–14 years, and 24 patients for 15–21 years). Out of the group with long-term follow-up for a mean period of 9·4 years 110 (58·5%) could be regarded as successfully irradiated, 36 (19·2%) had to have the eye enucleated and are still alive, and 42 (22·3%) died—18 (9·6%) of the latter from metastases and 24 (12·7%) from other causes (Fig. 3).

Out of the 24 patients who died from other causes four had to have the eye enucleated. Therefore, as

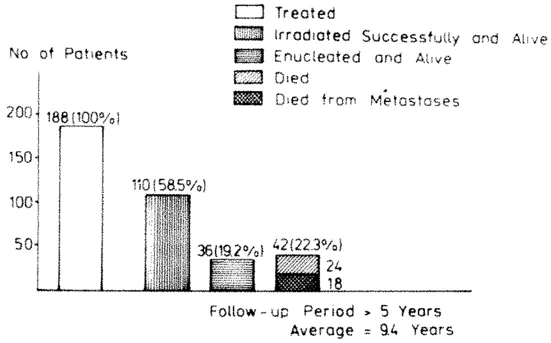


Fig. 3 *Long-term results after β irradiation with ^{106}Ru/^{106}Rh plaques of 188 patients.*

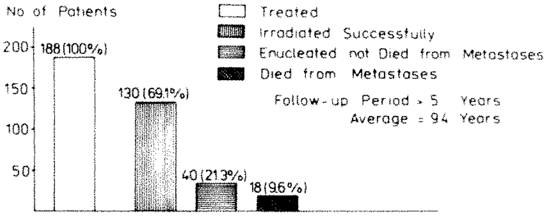


Fig. 4 *Long-term results after β irradiation with ^{106}Ru/^{106}Rh plaques of 188 patients.*

shown in Fig. 4, 130 (69·1%) patients could be regarded as successfully treated cases, 40 (21·3%) had to have the eye enucleated and are either alive or died from other causes than metastases, and 18 patients died from proved metastases.

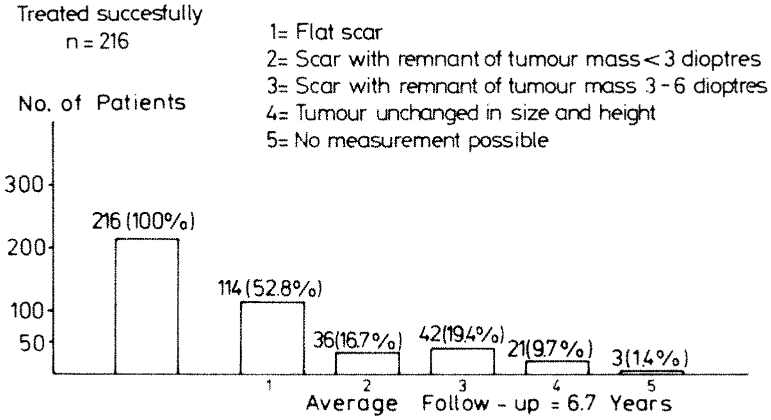
Tumour regression. As shown in Fig. 5, 114 (52·8%) of the successfully treated patients had a flat scar after therapy. The other eyes showed more or less evident remnants of the former tumour. The fact that tumour regression after this kind of therapy may take many months is important for avoiding a hasty decision to carry out enucleation. The regression to a flat, pigment stippled scar depends primarily on tumour size. However, all tumours larger than T1 NO MO (NO=no evidence of regional lymph node involvement; MO=no evidence of distant metastases) left behind an elevated mass, which should be observed carefully during the follow-up period because of some possible reactivation process (Figs. 6, 7).

Visual acuity. Preservation of useful visual acuity is a principal aim of β-ray treatment. As shown in Fig. 8, only 49 (22·7%) out of all successfully treated patients retained a good visual acuity of between 1·5–0·5. About half of the patients (54·2%) had only a poor central visual acuity of less than 0·2 because the macula had been involved in the cicatricial formation after treatment (Fig. 8). Visual field deficiencies corresponding to the retinochoroidal scar were recorded in all our patients.

Enucleation after β irradiation. Enucleation was necessary in 64 cases, mostly within the first year of treatment. The reason for removing the eye was new tumour growth in 54 and loss of visual acuity due to radiogenic side effects in 10 cases. Histological examination of the enucleated eyes showed active new-grown melanoma tissue without damage of the tumour cells in 52, scar tissue containing some tumour cells in four, scar tissue without tumour cells in four, and no reports of a histological examination were available in two cases. Out of all 64 the enucleated patients 11 (17·2%) died from metastases within one to seven years after enucleation; nine patients died from other causes.

Deaths after β irradiation. Seventy five patients of this series died during the follow-up period—40 of metastases, 27 of other diseases than melanoma (cardiac infarction or apoplectic stroke 19, other malignant tumours 6, cirrhosis of liver 1, suicide 1) and eight of unknown causes. Death from metastases was verified by necropsy in 19, laparoscopy in four,

Fig. 5 *Tumour regression after β irradiation.*



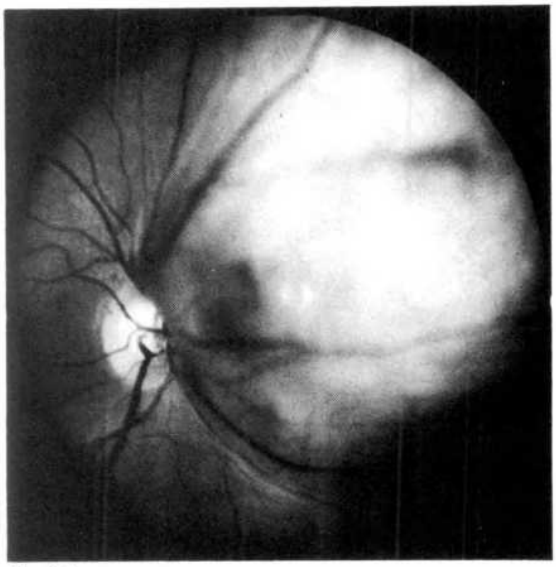


Fig. 6A

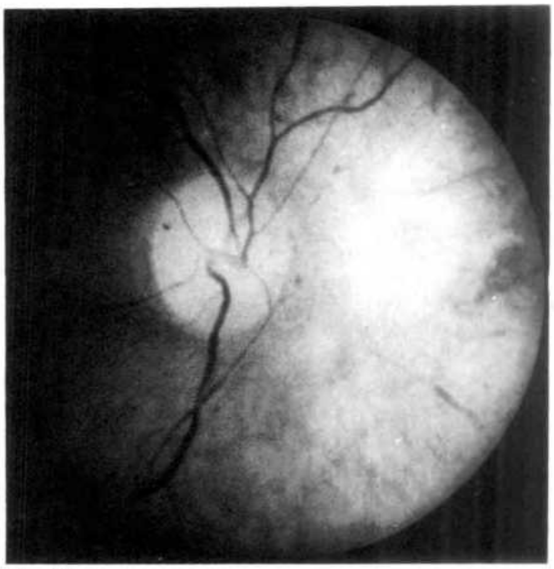


Fig. 6C

Fig. 6 A: *Choroidal melanoma of right eye before treatment.* B: *Same eye two years after β irradiation with ^{106}Ru/^{106}Rh 1084 Gy within 14 days at scleral surface.* C: *Same eye eight years after irradiation. Visual acuity 0·5.*

and by clinical examination in 17 cases. Metastases occurred mainly in the liver, where in some cases an extreme hepatomegaly was produced. 65% died within five years of irradiation.

Enucleation and metastases. Out of 64 patients enucleated because of tumour new growth after irradiation 11 (17·2%) died from metastases, whereas 29 (11·8%) patients out of the 245 cases without enucleation died from metastases.

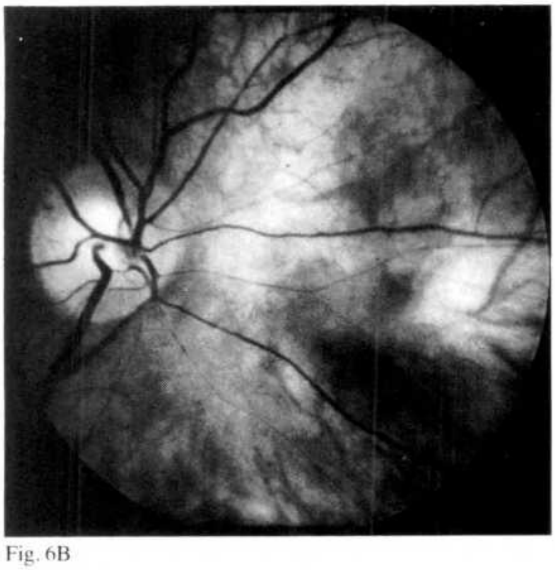


Fig. 6B

Tumour size. As shown in Fig. 9, most of the choroidal melanomas were class T1a or T1b (70·9%). The prevalence of smaller tumours is even clearer in the group of the 216 patients treated successfully (Fig. 10). In the group of 40 patients who later died from metastases or had to have the eye enucleated there was a prevalence of tumours of class T3 (17 cases, 42·5%). Only 10·5% of our patients who could be treated successfully with a follow-up period of more than five years had a melanoma classified as T3. This underlines the well-known correlation between tumour size and therapeutic outcome: the smaller the tumour the better the chance of treating choroidal melanomas successfully with β-rays.

Repeated radiotherapy. Repeated therapy with radioactive applicators was necessary in 16 cases because the tumour continued growing after the first irradiation. The second treatment was successful in seven patients. Nevertheless, four had to have the eye enucleated and five died from metastases.

β *Irradiation and xenon coagulation.* Light coagulation was additionally performed after β irradiation in 34 cases to occlude the choroidal vessels round the tumour. First, the central rim of the tumour was surrounded by coagulations. Later, if the tumour was not completely destroyed, the surface of the tumour proper was also coagulated. Especially in eyes with the melanoma close to the optic disc and where the applicator could not be placed completely round the tumour, we succeeded in a partially surrounding the central tumour rim with the effects of coagulation.

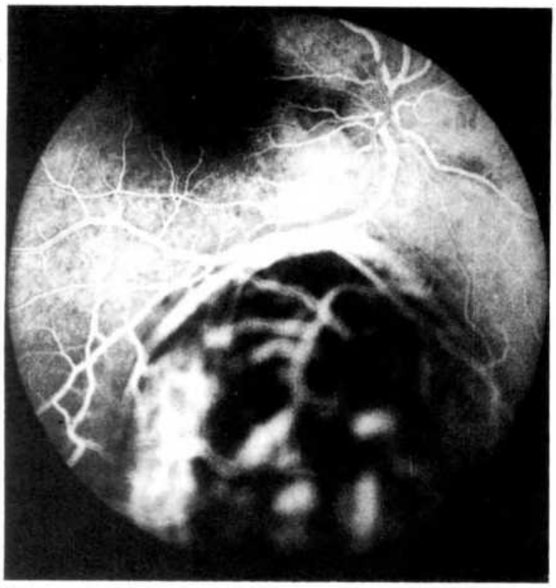


Fig. 7A

Fig. 7 A: *Choroidal melanoma of right eye before treatment, fluorescein angiography.* B: *Same eye six months after β irradiation with* ^{106}*Ru*/^{106}*Rh 1048 Gy within four days at scleral surface.* C: *Same eye five years after irradiation. Visual acuity 0·3.*

The results obtained in our 34 cases with light coagulation were as follows: patients successfully treated, 21; patients living but with eye enucleated, 4; patients dying, 9 (from metastases 4).

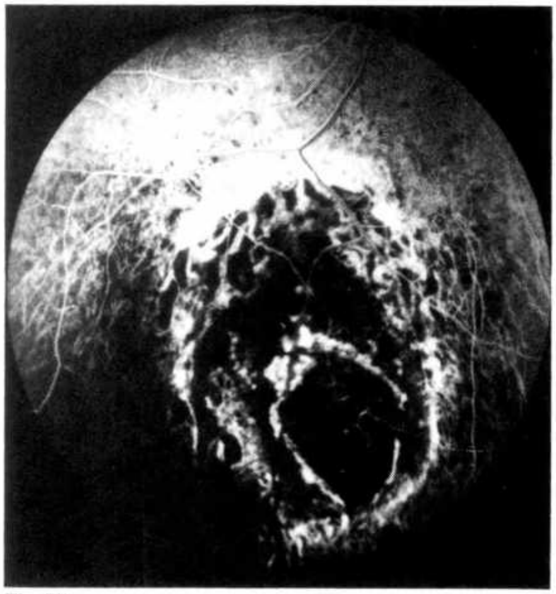


Fig. 7B

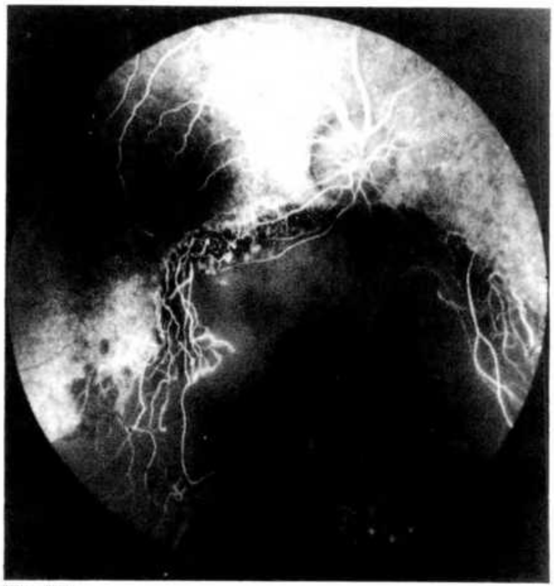


Fig. 7C

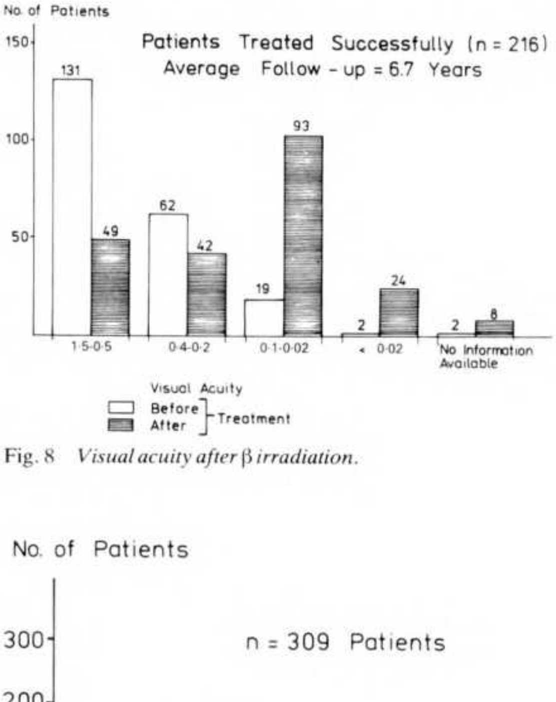


Fig. 8 *Visual acuity after β irradiation.*

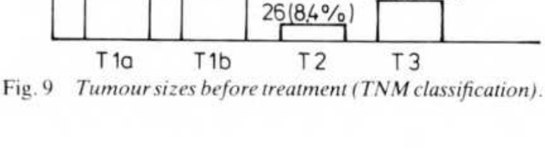


Fig. 9 *Tumour sizes before treatment (TNM classification).*

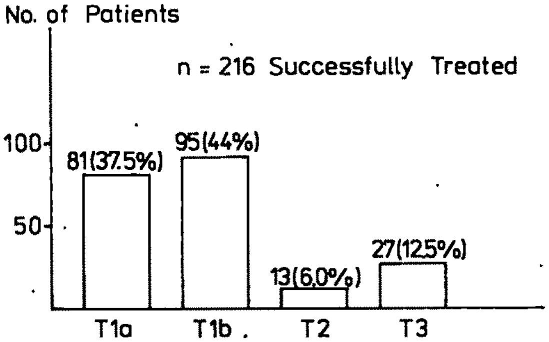


Fig. 10 *Tumour sizes before treatment of 216 successfully treated patients.*

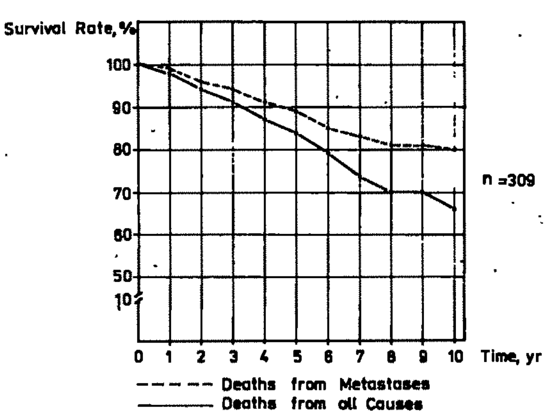


Fig. 11 *Survival rate of patients (n=309) with choroidal melanoma treated with ^{106}Ru/^{106}Rh β ray applicator. Broken line indicates deaths from metastases, solid line deaths from any causes.*

Radiogenic side effects. Radiogenic tissue damage must be expected after each kind of radiotherapy, particularly the serious late effects which may occasionally occur after β irradiation. Exudative reactions occurring a few days after irradiation, such as chemosis, choroidal detachment, and even transient retinal detachment, should not be regarded as serious complications, because of their good prognosis. Against earlier expectations the primary concern is now the postradiation retinopathy that has frequently followed β irradiation, sometimes even years after initially successful treatment.

Radiogenic complications which led to deterioration of visual acuity were as follows: macular destruction because of scarring around the tumour, 83; atrophy of the optic nerve, 23; macular degeneration, 16; postradiation retinopathy with oedema of the optic disc, 17; partial cuneiform cataract without loss of vision, 5; total cataract, 7; vitreous haemorrhage, 10; secondary glaucoma, 3; thrombosis of the central retinal vein, 2; scleral necrosis, 1; exudative reactions such as choroidal and retinal detachment with spontaneous improvement, 21.

Most of the patients (83) with a tumour 1 to 2 disc diameter away from the posterior pole showed a destruction of the macula, because the scarring round the tumour necessarily involved this retinal area.

Survival rate after ^{106}Ru/^{106}Rh therapy. The survival rate was calculated by the life table method. As shown in Fig. 11, survival rates of 84·3% (deaths from any causes) or 88·7% (deaths only from metastases) after five years and 65·8% (deaths from any causes) or 79·5% (deaths only from metastases) after ten years could be achieved. In this diagram the survival rates of patients who died from metastases and those who died from other causes were plotted separately. A comparison with results published in previous studies[6-8] shows that survival after local β irradiation is better than after enucleation.

Discussion

The traditional treatment of patients suffering from choroidal melanoma was enucleation of the involved eye as soon as diagnosis was made. More recently the value of enucleation has been questioned, and some authorities have even speculated that this procedure may impair prognosis.[9 10] This hypothesis has provoked objections,[11-13] so that additional studies will be needed to determine whether our ideas on the management of choroidal melanomas are correct.

Although in the past believed to be ineffective in the treatment of intraocular melanomas, radiotherapy has recently become more generally accepted, especially the use of radioactive plaques and charged particle irradiation.[14-16] Some investigators, including ourselves have shown that patients treated by conservative methods such as photocoagulation or irradiation as alternatives to enucleation have a relatively low incidence of metastases, but convincing randomised prospective studies are still lacking.[8]

The choice of therapy depends on certain conditions, and each case should be considered individually. In selecting the most effective therapeutic approach the following factors must be carefully weighed: size of the melanoma, its extent and location, its activity, the condition of the other eye, and the age, general health, and last but not least the psychological status of the patient.[17]

The results presented in this study lead us to the conclusion that β irradiation is an effective procedure especially for the treatment of small and medium sized choroidal melanomas (T1 and T2). Additional light coagulation or a second β irradiation make it possible to treat even larger tumours in two steps.

In previous studies[4-6] a 74% (1974), 61·6% (1979), and 64·4% (1983) cure rates were found. These results are in accordance with the therapeutic results after a long-term follow-up presented in this paper with a healing rate of 69·9%.

The apparent increase in the percentage of successfully treated patients from 64·4% (1964–80) to 69·9% in this paper may be related to the shorter follow-up of the most recent 104 patients, though the average follow-up of 6·7 years was longer in comparison with 5·4 years in the previous series. The slight differences between the percentages of the successfully treated cases in which the tumour regressed to a flat scar—45·5% (1980), 60·5% (1980) of patients observed for more than five years and 52·8% in this paper—are probably caused at random.

These figures suggest that β irradiation with ^{106}Ru/^{106}Rh plaques will produce a successful therapeutic outcome in about two-thirds of the cases, provided the following recommendations are observed. First, because of the physical properties of ^{106}Ru/^{106}Rh (at a distance of 6 mm, the dose received is less than 10% of the surface dose) the choroidal melanoma should not exceed 6 mm in height above the scleral surface. Tumour cells at a distance of more than 6 mm from the applicator will not receive the damaging dose of at least 1000 Gy (10 000 rad). Secondly, the distance of the posterior margin should be at least 1 to 2 disc diameters from the nerve head, otherwise radiogenic papillitis with atrophy of the optic disc will prevent useful visual acuity. Thirdly, if the tumour has involved the ciliary body (contrary to former opinion) a special shape of ^{106}Ru/^{106}Rh plaque can be used with some success. Fourthly, there should be no extension of tumour outside the eye.

Radiogenic side effects and the incidence of complications depend on the dose distribution within the eye. In the case of β irradiation the severity and extension of postradiation retinopathy is less than after ^{60}Co irradiation, with its higher volume dose.[18] The high incidence of visually destructive radiation effects after β irradiation was caused by macular destruction in those cases where the tumour grew close to the macular region. If the tumour comes closer than 2 disc diameters to the optic disc, the dose delivered to the nerve head will result in an increasing incidence of optic atrophy even after ^{106}Ru/^{106}Rh plaque therapy.

Although it is evident from these and other statistical data that survival rate and local therapeutic results are mainly dependent on the number of tumour cells within the eye, it may sometimes be necessary to irradiate larger tumours because the patient refused enucleation or the tumour occurred in the only eye able to see. In some of these cases I have observed against expectation a surprising shrinkage of the tumours. In questionable situations, therefore, it seems to be justified to try β irradiation first and to hope for regression before performing enucleation.

My experience suggests that local irradiation is not likely to result in a higher incidence of metastases than enucleation, though the only scientific way to answer this question would be a randomised prospective study. Rotman *et al.*[19] pointed out that those methods of treatment which left the eye in situ (local excision, light coagulation, radioactive applicators) had a greater overall survival rate than enucleation of the eye. A further suggestion is that sterilisation of the tumour by irradiation, in contrast to enucleation, promotes an immune response that may indeed control distal metastasis.[20]

New radiotherapeutic procedures have been published recently that improve the possibilities of local radiotherapy by ^{125}I seeds[14] and proton beam irradiation[14] or heavy helium ions.[15] Although long-term follow-up examinations are still lacking, the preliminary experience with these new methods is encouraging. The management of choroidal melanomas will probably remain controversial in the near future. In any case β irradiation with ^{106}Ru/^{106}Rh plaques adds to the possibilities of treating choroidal melanoma.

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Cyclosporin A: tissue levels following topical and systemic administration to rabbits

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SUMMARY Plasma and aqueous levels of cyclosporin A (CsA) were determined following topical administration of CsA 1% to healthy rabbit eyes and compared with levels obtained when administered to rabbit eyes which had received corneal grafts 7–10 days previously. In addition plasma levels were determined following intramuscular administration of 50 mg CsA and the results compared with those obtained following topical administration. Topical administration to healthy rabbit eyes five times a day for three days resulted in plasma levels of CsA which were similar to those obtained over three days following an intramuscular administration of 50 mg CsA. The plasma levels in both were significantly higher than those obtained following topical administration to rabbit eyes which had received corneal grafts 7–10 days previously. Aqueous levels of CsA were lower than plasma levels, and there was no significant difference between levels obtained when CsA was administered topically to healthy eyes, to eyes which had received corneal grafts, or to the fellow eye.

Cyclosporin A (CsA) has been shown in a number of animal investigations to be effective in prolonging the survival or corneal grafts when administered intramuscularly, topically to the eye which had received the graft, or when given as a retrobulbar injection.[1-7]

It has been suggested that when administered topically the drug may act locally.[3-7] In support of this it has been reported that the survival time of corneal grafts in five rabbits was not prolonged when the CsA was administered topically to the other eye.[7] It is surprising that this result was obtained, because therapeutic levels of CsA were detected in the plasma.

We decided to investigate further the plasma and aqueous levels of CsA following topical administration to rabbit eyes and to compare them with those obtained when CsA was administered intramuscularly. We considered it was important to determine the tissue levels obtained after topical administration to eyes which had recently received corneal grafts, as CsA is known to be particularly effective when administered during the first few days following an allogeneic graft.[8 9]

Materials and methods

CYCLOSPORIN A

Cyclosporin A (Sandoz) was dissolved in arachis oil in a concentration 1 g/100 ml (=10 g/l). The solution was heat sterilised and prepared in 10 ml bottles.

ANAESTHESIA

The animals were anaesthetised with intramuscular 'Hypnorm' (fentanyl citrate and fluanisone) 1 ml/kg. Adequate neuroleptanaesthesia was obtained to enable cornea grafts to be performed and to allow removal of samples of aqueous and blood.

CORNEAL GRAFTING

New Zealand white rabbits were killed, and 6·0 mm donor penetrating corneal grafts were trephined. Dutch rabbits of weight 2 kg were used as recipients. Guttae cyclopentolate 1% and guttae phenylephrine 10% were instilled into the eye. 10 000 units of heparin was administered intravenously to prevent aqueous clotting. The superior and inferior recti muscles were secured with 6/0 silk sutures. A 5·5 mm central corneal button was trephined. The 6·0 mm donor button was sutured with eight interrupted 10/0 nylon sutures. Further sutures were added if

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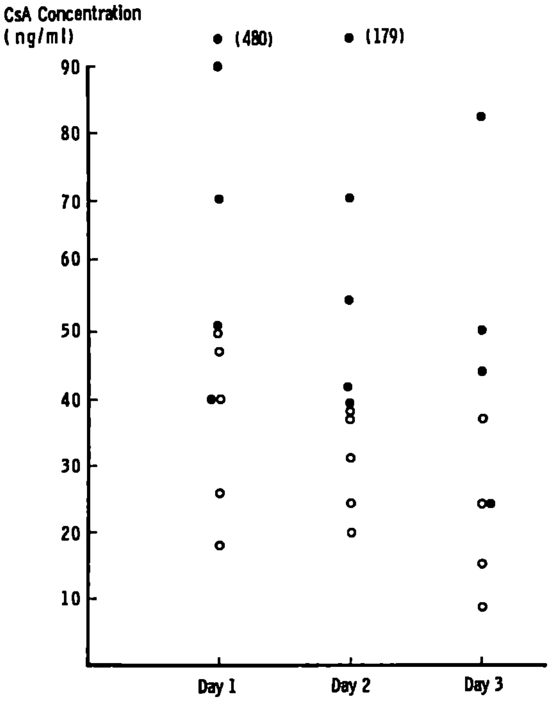

Fig. 1 *Plasma and aqueous levels of CsA obtained following topical CsA five times a day to healthy eyes. Samples were obtained daily. The solid spots indicate plasma levels and the open circles aqueous levels. (SI conversion: ng/ml=μg/l.)*

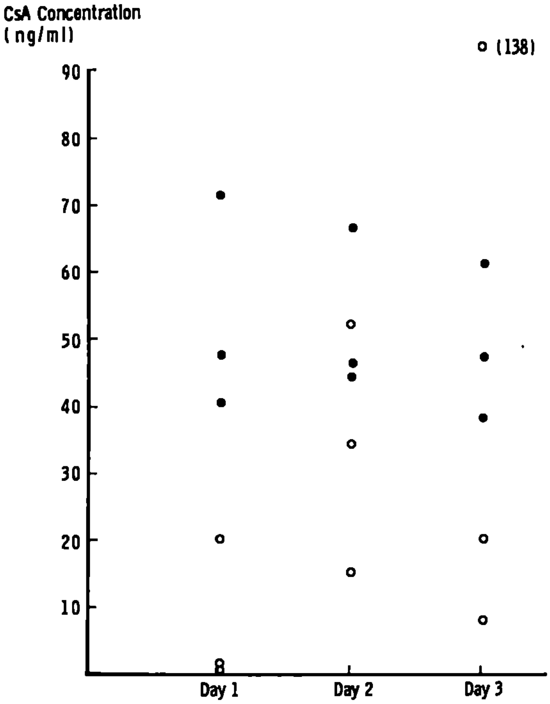

Fig. 2 *Plasma and aqueous levels of CsA following topical CsA five times a day to healthy eyes. Samples were obtained daily; aqueous was obtained from the fellow eye. The solid spots indicate plasma levels and the open circles aqueous levels.*

required, and the anterior chamber was reformed with air. Guttae chloramphenicol 0·5% was instilled and 1 mega unit of penicillin was injected intramuscularly. The lids were closed with a tarsorrhaphy stitch.

SAMPLING OF AQUEOUS AND PLASMA

Each rabbit was anaesthetised and a 25 gauge needle was inserted into the anterior chamber. 0·25 ml of aqueous was removed. Any sample contaminated with blood was discarded. 1 ml of blood was removed from a vein in the ear of the rabbit. Each sample was placed into a lithium heparin tube. The tubes containing blood were left at room temperature for two hours to allow CsA to equilibrate between red cells and plasma. Plasma was then separated and frozen until the assay was performed. The radioimmunoassay[10] was performed with a kit provided by Sandoz Ltd, and the accuracy of the assay was monitored by control samples where the concentration of CsA was known.

ADMINISTRATION OF CSA

The topical instillation of CsA 1% comprised 2 drops, (100 μl). Topical CsA was administered five times a day. The intramuscular administration comprised 5 ml CsA 1% containing 50 mg CsA.

Experiment 1. CsA 1% was administered topically five times a day for three days to healthy rabbit eyes. Samples of plasma and aqueous from the same eye

Table 1 *Average plasma and aqueous concentration of CsA following topical and systemic administration*

	No. of rabbits	*Mean plasma concentration ng/ml*	*Mean aqueous concentration ng/ml*
Topical CsA to healthy rabbit eye. Aqueous sampled from the same eye	5	116	27
Topical CsA to healthy rabbit eye. Aqueous sampled from fellow eye	3	51	18
Topical CsA to rabbit eye with a corneal graft. Aqueous sampled from the same eye	6	28	23·5
Intramuscular CsA 50 mg to rabbit. Plasma sampled daily. Aqueous not sampled	3	48·3	—

SI conversion: ng/mg=μg/l.

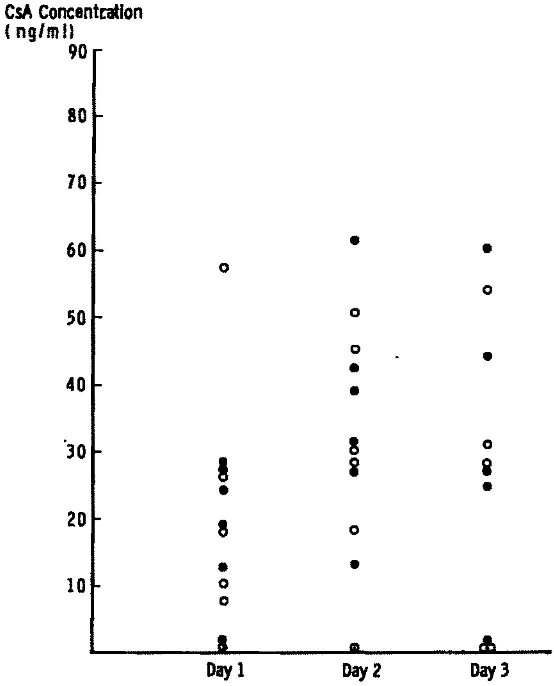

Fig. 3 *Plasma and aqueous levels of CsA obtained following topical CsA five times a day to eyes bearing a corneal graft. Samples were obtained daily. The solid spots indicate plasma levels and the open circles aqueous levels.*

were obtained daily, and the CsA levels determined. n=5.

Experiment 2. CsA 1% was administered topically five times a day for three days to healthy rabbit eyes. Samples of plasma and aqueous from the fellow unoperated eye were obtained daily and the CsA levels determined. n=3.

Experiment 3. CsA was administered topically five times a day for three days to rabbits which had received a corneal graft 7–10 days previously. Samples of plasma and aqueous from the eye containing the graft were obtained daily and the CsA levels determined. n=6.

Experiment 4. An intramuscular injection of 50 mg CsA was administered to each of three rabbits. Samples of plasma were obtained subsequently daily for three days and the CsA levels determined. n=3.

Results

Figs. 1–3 demonstrate the plasma and aqueous levels of CsA following the topical administration of CsA, and Fig. 4 the plasma level of CsA obtained on three days following single intramuscular injection of 50 mg CsA. Table 1 demonstrates the average plasma and aqueous levels of CsA obtained.

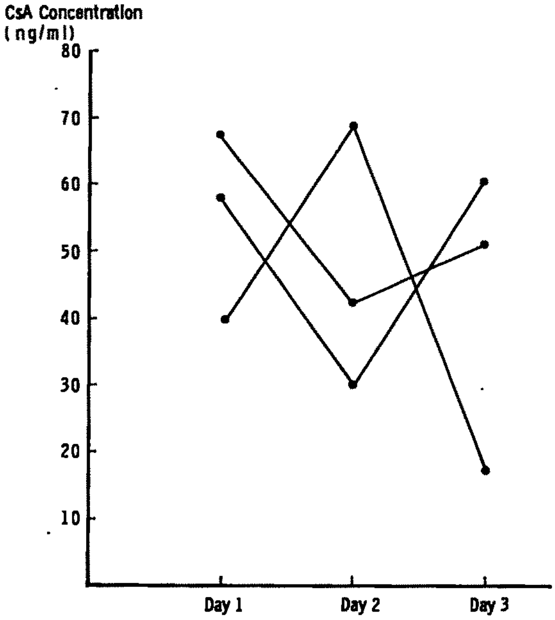

Fig. 4 *Plasma levels of CsA obtained on the three days following an intramuscular injection of 50 mg CsA.*

The plasma levels of CsA following topical administration to healthy eyes (Figs. 1, 2) were significantly higher ($p<0{\cdot}01$, Wilcoxon rank test) than the plasma levels following topical administration to eyes which had received corneal grafts (Fig. 3).

There was no significant difference between the plasma levels of CsA measured over the three days following an intramuscular injection of 50 mg, CsA (Fig. 4) and the plasma level measured daily on the rabbits which received topical CsA five times a day to healthy eyes (Figs. 1, 2) (Wilcoxon rank test).

The plasma levels of CsA within the group which received the intramuscular CsA (Fig. 4) were significantly higher than the plasma levels in the group which received topical CsA five times a day to the eye which had received the corneal graft (Fig. 3) ($0{\cdot}02>p>0{\cdot}01$, Student's *t* test). There was no significant difference between the aqueous levels shown in Figs. 1, 2, and 3.

Discussion

The investigation confirms the findings by Foets *et al.*[17] that systemic levels of CsA are recorded when CsA is administered topically to rabbit eyes. A single intramuscular injection of 25 mg/kg CsA results in a plasma level which is less than that normally considered therapeutic, namely >100 mg/l.[11] This plasma level tends to persist at least over three days.

Aqueous levels of CsA following topical administration are lower than plasma levels and appear to be uninfluenced by the presence of a corneal graft or when the CsA is administered to the other eye.

As the plasma level of CsA following topical administration to healthy rabbit eyes is found to be similar to that following an intramuscular injection of CsA, this suggests that sufficient CsA is absorbed to act systemically. As less CsA is absorbed when administered topically in the early postgraft period, then clearly the conditions do not favour absorption, as might be expected, but reduce the absorption.

It is possible that topical administration in the early postgraft period is ineffective, as the absorption is reduced. It should be noted that, when Foets *et al.*[7] administered CsA topically to the fellow eye in a rabbit which had received a corneal graft, the fellow eye had also been operated on. It is possible that the failure to prevent rejection may have been due to poor absorption of CsA from the injured fellow eye in the early postgraft period. Topical administration of CsA to an uninjured eye would appear in the animal model to be a potentially useful mode of administering CsA. Clearly further investigation is required to determine whether this is true in the human. In relation to corneal grafting, unless clear evidence of a local action can be demonstrated, it is possible it may be of little use in the early postgraft period. Administration to the unaffected eye or systemic administration would appear to be more suitable methods of giving the drug during this important period.

We gratefully acknowledge assistance from Mr A J Bron, Nuffield Laboratory of Ophthalmology, Oxford, Professor P J Morris, Nuffield Department of Surgery, Oxford, and Dr J F Borel of Sandoz Ltd.

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Arteriovenous communication of the iris

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SUMMARY A case of arteriovenous communication of the iris in the left eye of a 45-year-old man is reported. The haemodynamic changes and differential diagnosis of this kind of communication are briefly discussed.

Haemangiomas of the iris are extremely rare.[1-4] They are usually capillary[1,3,5,6] or cavernous haemangiomas[1,7,8] but so-called racemose haemangiomas are observed very rarely.[9] This lesion is not a true tumour but a vascular anomaly. It consists of abnormal, direct, bypassing capillary bed communications between more or less fully developed, dilated, and tortuous arteries and veins.[10,11] Some authors have therefore recently suggested that the term racemose haemangioma or racemose aneurysm should be replaced by arteriovenous communications[12] or arteriovenous anastomoses.[11]

It seems that arteriovenous communications are a congenital anomaly.[11] Their pathogenesis is unknown, but they probably arise from a local defect in the maturation of the primitive mesenchymal cells. In the early stages of development of the vascular system, for example in the retina, primitive mesenchymal cells differentiate into solid cords of endothelial cells which gradually become canalised to form a primitive capillary network.[11] As blood enters this network, the primitive vessels develop into arteries, veins, and connecting capillaries, with the simultaneous retraction and atrophy of some primitive capillaries.[13] In arteriovenous communications extensive capillary retraction and atrophy may occur, with development of a single channel to shunt blood across this defective capillary zone.[12]

Because of their slow development, arteriovenous communications are usually encountered for the first time in the second or third decade of life.[9,11] Lesions occur mainly in the retina,[4,11,12] and less frequently in the orbit, conjunctiva, and sclera.[4,14-17] There are very few reports of arteriovenous communications in the iris.[9] In view of the rarity of this lesion the case described here was considered worth reporting.

Case report

A 45-year-old man was admitted to this clinic because of a vascular anomaly of the left iris. The patient said he had noticed red spots on the iris about 15 years before. As he had no disturbance of vision, he did not consult an ophthalmologist.

Ocular examination showed: in the right eye, visual acuity 1·0, IOP 15 mmHg, anterior segment and fundus normal, visual field normal; in the left eye, visual acuity 1·0, IOP 15 mmHg. A dilated episcleral vessel coursing towards the corneal limbus was seen at 2 o'clock (Fig. 1). It entered the sclera at 3 o'clock

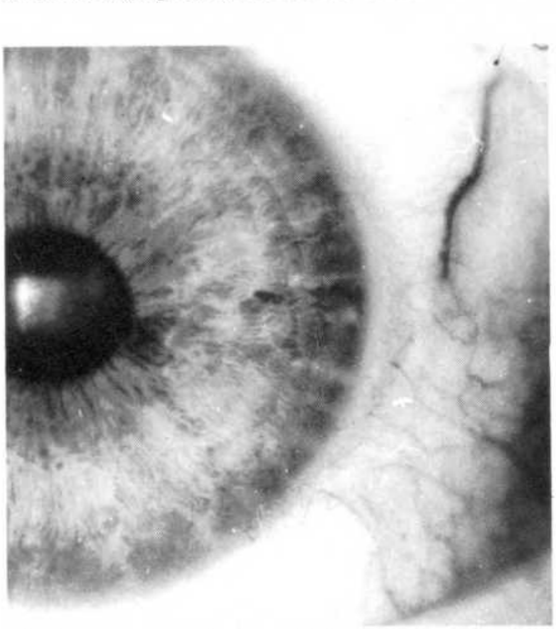

Fig. 1 *Appearance of sclera and iris with arteriovenous communication.*

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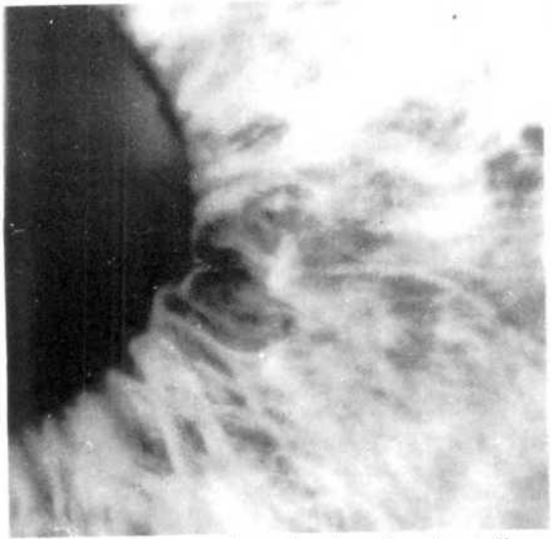

Fig. 2 *Conglomerate of convoluted vessels at the pupillary border.*

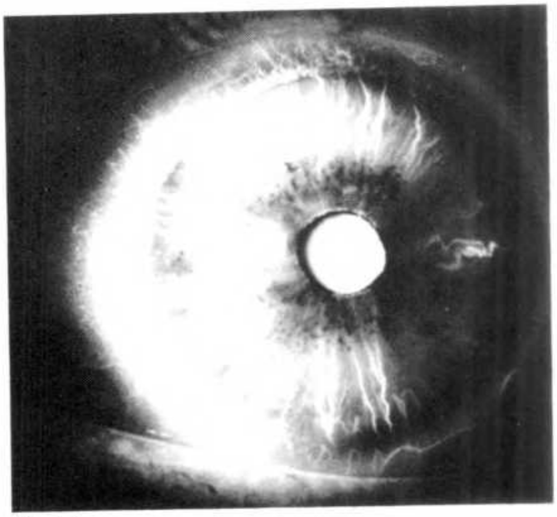

Fig. 3 A

Figs. 3 ABC *Fluorescein angiography of arteriovenous communication of the iris. Note sequence of filling of communication with fluorescein and small blurring (Leakage?) of vessels at the pupillary border.*

1 mm from the limbus. The dilated vessel could be seen subsequently gonioscopically in the anterior chamber angle, and it entered the surface layers of the iris stroma. After entering the angle the vessel became wider and more tortuous as compared with its episcleral segment. It then coursed towards the pupillary border of the iris, where it formed a conglomerate of greatly dilated and tortuous vessels (Fig. 2). Above this vessel another one slightly less dilated and tortuous could be seen. From the conglomerate of vessels at the pupillary border of the iris a dilated and tortuous vessel emerged, the course of which was only partially seen because it penetrated deeper into the iris stroma. This vessel disappeared within the anterior chamber angle and reappeared as a dilated episcleral vessel in the corneal limbus. No other ocular changes were found besides those described within the anterior segment. The visual field was normal.

Fluorescein angiography of the iris enabled us to delineate accurately the course of the altered vessels and to determine the afferent and efferent part of the communication (Figs. 3A, B, C). The dilated and tortuous iris vessel at 3 o'clock was the first to fill.

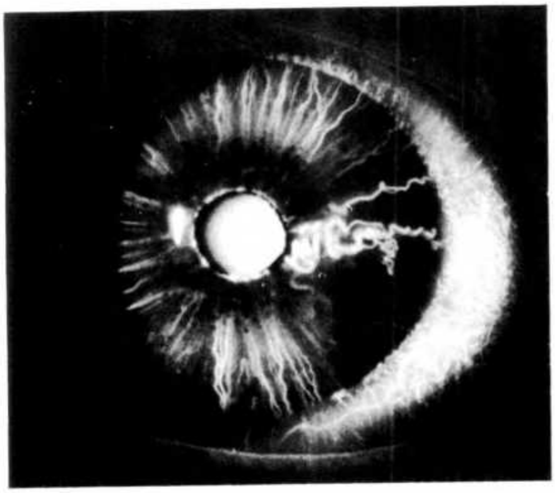

Fig. 3 B

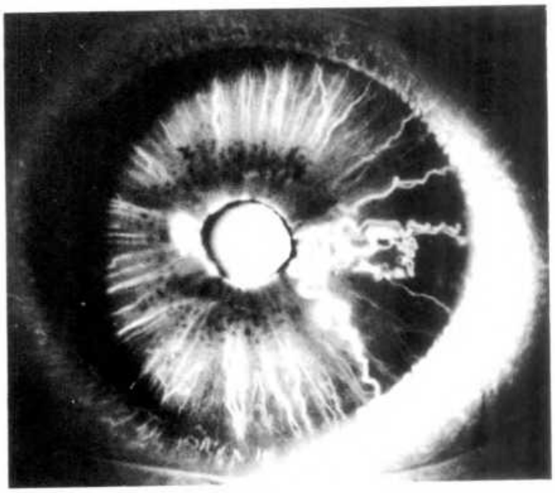

Fig. 3 C

This vessel then divided into several branches which in their course formed a conglomerate of greatly dilated and tortuous vessels. They were seen not only in the peripupillary part of the iris but also in its medial part, which could not be seen in the slit-lamp. At 2 o'clock a slightly dilated vessel was observed which filled with fluorescein slightly later than the vessel at 3 o'clock. From the vessel conglomerate at the iris margin a dilated vessel emerged which coursed towards the corneal limbus at 5 o'clock. In the part of the iris in which the anomaly occurred the vessels filled later than in the other parts. Moreover in that part fewer vessels were shown up by fluorescein even in the late phases of the examination. During the examination a small leakage of dye from the vessels forming the arteriovenous communication could be observed. However, this leakage may have been at least in part an artefact owing to the vessels of the iris being slightly out of focus in the camera. Such artefacts have been reported.[18] Fluorescein angiography of the left fundus was normal.

When the intraocular pressure was increased by means of the ophthalmodynamometer, pulsation of the arteriovenous communication as well as of the afferent and efferent vessels could be observed at a pressure above 90 mmHg.

Neurological examination did not show any alterations indicating changes in the central nervous system. The patient was therefore not considered suitable for carotid angiography.

Discussion

The lesion found in this patient corresponds to the arteriovenous communications usually observed within the retina.[11 12] As in the retina, dilated afferent and efferent vessels, which had already been noted in the episclera, as well as a mass of convoluted channels between them could also be distinguished here. The appearance of this vascular disorder, as well as the fact that pulsation of the afferent and efferent vessels occurred almost at the same level as the raised intraocular pressure, indicates that this arteriovenous communication can be included in group 2 of the classification of Archer *et al.*[12] The angiographic evidence of slight leakage of fluid from the vessels involved as well as of reduced perfusion of the iris in the sector where the lesion lay, pointed to the existence of some, though not intense, decompensation of the arteriovenous communication. It accounts also for the fact that this communication can be included in group 2 of Archer *et al.*[12] Because of the small number of reported cases of arteriovenous communications in the iris it is of course difficult to say whether the division into three groups introduced for pathological alterations in the retina will also apply to lesions in the iris.

In the available literature only a few descriptions of this kind of lesion in the iris have been found. A similar case to that presented here was described by Stur and Strasser.[9] A case presented by Ida Mann[19] which was diagnosed as congenital angioma of the iris may also have been one of arteriovenous communication. A case of vascular anomaly of the iris was also described by Savir and Manor,[20] but, since that abnormality did not have afferent and efferent vessels, it cannot be regarded as an arteriovenous communication.

Arteriovenous communications of the iris need to be differentiated mainly from secondary vascular alterations occurring in the course of various diseases of the iris.[21] Dilated and tortuous vessels of the iris are observed in association with cysts and melanomas of the iris.[21] Other lesions, such as rubeosis iridis or microhaemangiomas of the pupillary border[22 23] can be easily distinguished from arteriovenous communications.

Owing to the asymptomatic course of the disease in the patient reported on here no treatment was applied. If complications arise, such as spontaneous hyphaema, the possibility of performing photocoagulation can be considered.

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Comparison of K-Sol and M-K medium for cornea storage: results of penetrating keratoplasty in rabbits

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SUMMARY Five pairs of rabbit corneas were stored for two weeks at 4°C, one of each pair in K-Sol medium, and one in McCarey-/Kaufman (M-K) medium. After transplantation all penetrating keratoplasty grafts became clear and thin. Endothelial cell loss was significantly less in the K-Sol stored corneas. Another five pairs of corneas were stored for two weeks in K-Sol or three days in M-K medium. After penetrating keratoplasty there were no significant differences in clarity, thickness, or endothelial cell loss. The results indicate that K-Sol provides satisfactory medium-term corneal storage compared with short-term storage in M-K medium at refrigerator temperatures.

K-Sol, a new corneal preserving medium, which contains TC-199, 2·5% chondroitin sulphate, and HEPES buffer, has been tested for medium-term storage of donor corneas for two weeks with satisfactory results.[1 2] The present study was designed to compare K-Sol and M-K medium preservation of endothelial cell viability in rabbit corneas after penetrating keratoplasty.

Materials and methods

TWO-WEEK STORAGE IN K-SOL AND M-K MEDIUM

Animal care and treatment in this investigation were in compliance with the ARVO resolution on the use of animals in research. Five New Zealand white rabbits, 2–3 kg body weight, were killed with an overdose of intracardiac pentobarbital. Paired corneas with 2 mm of scleral rim were excised by means of standard eye bank procedures. Endothelial cell density was determined by specular microscopy. One cornea from each rabbit was stored in K-Sol (Cilco), and the fellow cornea was stored in M-K medium, both at 4°C. Gentamicin (100 μg/ml (100 mg/l) was added to both preserving solutions. After two weeks the paired corneas were used for penetrating keratoplasty. A 7·5 mm donor button was trephined from the endothelial side, and the graft was transplanted into a 7·0 mm recipient bed and sutured with 10–0 nylon. One eye of each of five rabbits received a cornea stored in K-Sol and the fellow eye received the mate cornea, stored in M-K medium. After surgery 1% atropine and gentamicin ointment were applied daily for three days.

Postoperative examinations included slit-lamp biomicroscopy to evaluate graft clarity and the measurement of central graft thickness by ultrasonic pachymetry (Acutome corneometer; 1640 m/s) on days 1, 3, 5, 7, and 14. On day 14 the rabbits were killed by an overdose of pentobarbital and the corneas obtained and stored in the original preserving medium until the cells were counted. Endothelial cell density was determined by three independent observers, each of whom counted cell densities in three different 1 mm² areas. All examinations, as well as the surgery, were performed in a masked fashion.

TWO-WEEK STORAGE IN K-SOL, THREE-DAY STORAGE IN M-K MEDIUM

Paired corneas from five rabbits were used. One cornea from each pair was stored in K-Sol for two weeks and the fellow cornea was stored in M-K medium for three days, both at 4°C. The surgical procedure and postoperative examinations were identical to those described above.

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Results

TWO-WEEK STORAGE IN K-SOL AND M-K MEDIUM

Both groups of grafts were oedematous on the first postoperative day: 0·565±0·08 mm for those stored in K-Sol, and 0·587±0·06 mm for those stored in M-K medium (± here and below denotes standard error of the mean). Swelling decreased rapidly. By day 3 corneal thickness was 0·400±0·03 mm in the K-Sol group and 0·410±0·04 mm in the M-K group (Fig. 1). All the grafts continued to decrease in thickness thereafter, but differences between the two groups were not statistically significant at any time.

All but one of the grafts were clear after day 5. One rabbit with a graft stored in K-Sol had broken sutures over one quadrant and the anterior chamber was filled with fibrin clots on day 7. During an attempt to remove the fibrin clots and repair the wound the lens was ruptured, with vitreous prolapse. The lens material was removed and anterior vitrectomy performed, after which the wound was repaired successfully. On day 14 the graft was still oedematous, with a corneal thickness of 0·51 mm; the graft in the fellow eye remained clear. The graft in the damaged eye cleared on day 21, at which time cell densities were determined in both eyes of this rabbit. Endothelial cell density was higher in the K-Sol stored eye than in the fellow eye with the M-K medium-stored donor tissue (Fig. 2).

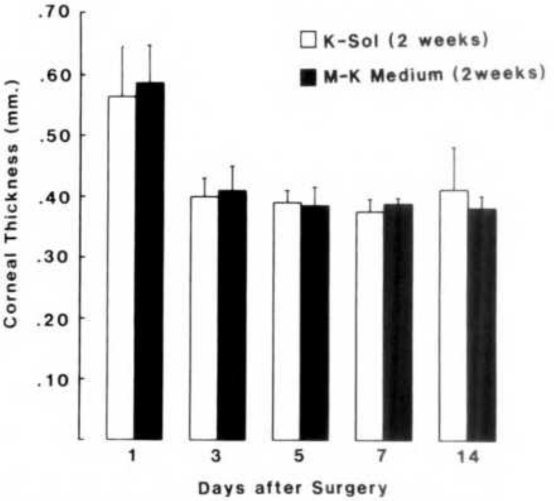

Fig. 1 *Change of central corneal thickness after surgery. Two weeks storage in K-Sol and M-K medium. One cornea of this group needed resuturing on the eighth postoperative day.*

Endothelial cell loss averaged 24·2% in the K-Sol

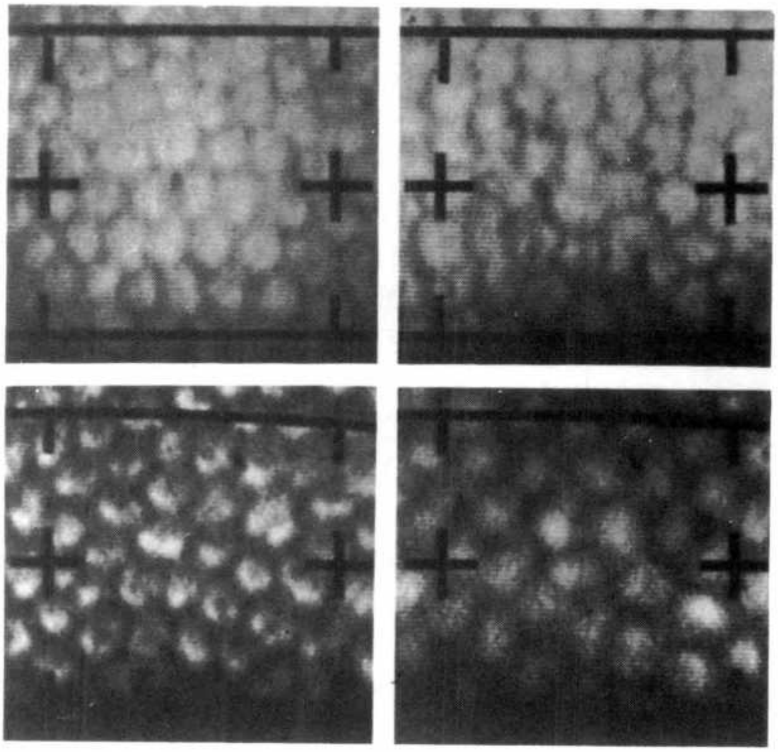

Fig. 2 *Specular microscopy of endothelial cells preoperatively and three weeks after surgery. Right: Cornea stored in K-Sol for two weeks. Repair of wound dehiscence after lens extraction and anterior vitrectomy. Cell density before surgery=3900/mm^2 (above), after surgery=3000/mm^2 (below). Cell loss=23%. Left: Fellow cornea stored in M-K medium for two weeks. Cell density before surgery=3800/mm^2 (above), after surgery=2400/mm^2 (below). Cell loss=36·8%.*

Table 1 *Endothelial cell density (cell/mm²) before and after surgery. Donor corneas stored for two weeks*

	Storage in K-Sol (14 days)			*Storage in M-K medium (14 days)*		
Rabbit no.	*Before surgery*	*After surgery*	*% Cell loss*	*Before surgery*	*After surgery*	*% Cell loss*
4135	3400	2400	29·4	3300	2100	36·3
4029	3300	2400	27·3	3300	2100	36·3
4124	3900	3000	23·1	3800	2400	36·8
4138	3200	2700	15·6	3300	2300	30·3
4119	3500	2600	25·7	3700	2800	26·4

Cell loss in M-K stored corneas significantly higher than in K-Sol stored corneas (p=0·023). Paired Student's *t* test.

Table 2 *Endothelial cell density (cell/mm²) before and after surgery. Donor corneas stored in K-Sol for two weeks or in M-K medium for three days*

	Storage in K-Sol (14 days)			*Storage in M-K medium (3 days)*		
Rabbit no.	*Before surgery*	*After surgery*	*% Cell loss*	*Before surgery*	*After surgery*	*% Cell loss*
4118	3200	2600	18·7	3500	2500	28·5
4128	3700	3100	13·5	3800	2800	26·3
4127	3700	2400	35·1	3600	2700	25·0
4145	3300	3100	6·1	3300	2900	12·1
4122	3300	2500	24·2	3300	2200	33·3

Cell loss not significantly different in the two groups. Paired Student's *t* test.

group and 33·2% in the M-K medium group (Table 1). The difference was statistically significant (p=0·023).

TWO-WEEK STORAGE IN K-SOL, THREE-DAY STORAGE IN M-K MEDIUM

On the first postoperative day all grafts were oedematous; the K-Sol group was slightly thicker than the M-K medium group (Fig. 3). Both groups of grafts thinned rapidly, and all grafts were clear and less than 0·4 mm in thickness on day five. Differences in thickness between the two groups were not significant.

Endothelial cell loss in four of the five K-Sol stored grafts was slightly less than the M-K stored grafts but the differences were not statistically significant (Table 2, Fig. 4).

Discussion

M-K medium, which contains TC-199, HEPES buffer, and dextran, has been widely used to preserve donor corneal tissue in eye banks all over the United States. However, M-K medium is a short-term storage solution, with a maximum preservation time of 72 hours depending on the condition of the donor tissue prior to storage.[3,4] Prolonged preservation in this medium is not recommended. Early studies by Van Horn *et al.*[5] showed more than 20% cell death in cat corneas after five days of storage in M-K medium.

K-Sol contains TC-199, HEPES buffer, and chondroitin sulphate. In studies comparing chondroitin sulphate and dextran in preservative media Schimmelpfennig found that 5% chondroitin sulphate reduced endothelial cell damage in human eyes, compared with 5% dextran, after one or two weeks of

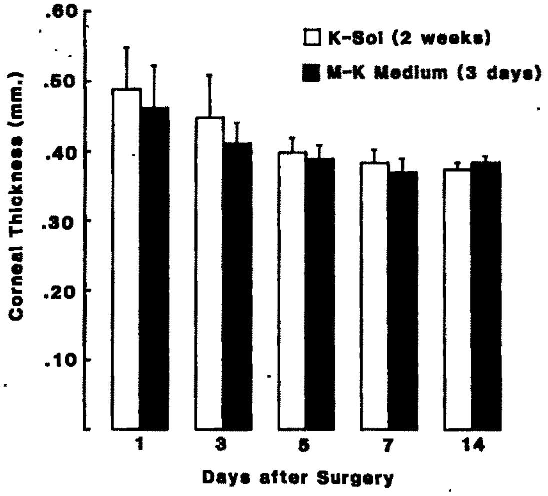

Fig. 3 *Change in corneal thickness after surgery. Corneas were stored in K-Sol for two weeks or M-K medium for three days.*

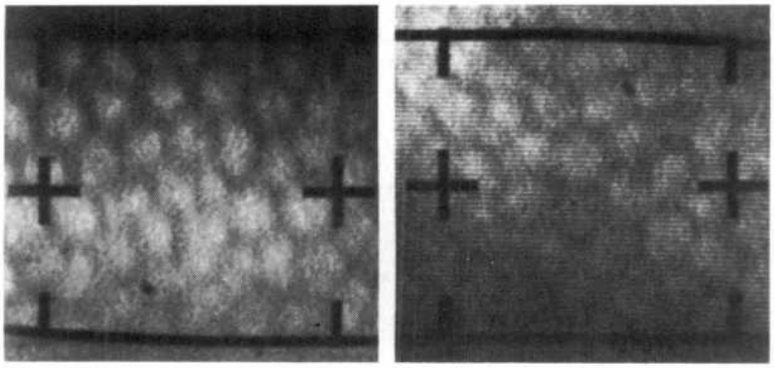

Fig. 4 *Specular microscopy of endothelial cells two weeks after surgery. Preoperative cell density in both corneas = 3300/mm^2. Right: Cornea stored in K-Sol for two weeks. Cell density after surgery = 3100/mm^2. Cell loss = 6·1%. Left: Fellow cornea stored in M-K medium for three days. Cell density after surgery = 2900/mm^2. Cell loss = 12·1%.*

storage.[6] Stein *et al.* also found that 1·5% chondroitin sulphate gave excellent endothelial preservation for two weeks.[7] In our previous studies we found that 2·5% chondroitin sulphate is the optimal concentration for corneal storage.[1] The osmolality of K-Sol is 310 mOsm, and the pH is maintained at 7·4 by HEPES buffer, which has also been determined to be optimal for corneal preservation.[8,9]

In the present study two weeks of storage in K-Sol and M-K medium followed by penetrating keratoplasty demonstrated no differences in corneal deturgescence and graft clarity, but significantly less endothelial cell loss in the K-Sol group. In their study of penetrating keratoplasty in rabbits Bigar *et al.*[10] obtained clear grafts from donor corneas stored in M-K medium up to 14 days. In our study, after 14 days of storage in M-K medium, all grafts were also clear, and the average endothelial cell density was still adequate to maintain healthy corneas (2225 cells/mm^2). However, our quantitation of endothelial cell loss in the early postoperative period indicates that K-Sol provided better preservation of endothelial cells than M-K medium over a two-week period, and at least comparable preservation for 14 days compared with three-day M-K storage.

In spite of the fact that rabbit corneal endothelium is capable of cell division and regeneration it is important to note that, in this study, even 14 days after surgery there was still a significant difference in endothelial cell densities in the groups that received corneas stored for two weeks in the two media. It seems probable that this difference can be attributed to improved preservation of the endothelial cells stored in K-Sol compared with those stored in M-K medium for this medium-term interval. The fact that the K-Sol stored graft with the broken suture survived with less cell loss than the fellow eye implies that corneas stored in K-Sol for two weeks can tolerate severe surgery with no long-lasting ill effects. Further investigation in humans is needed to confirm these findings.

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Adenosquamous carcinoma of the lacrimal caruncle: a case report

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SUMMARY A 76-year-old Caucasian woman presented with a caruncle tumour, histologically diagnosed as mixed adenosquamous carcinoma. Complete excision was performed, but this necessitated removing parts of the lacrimal canaliculi. No local recurrence or distant metastasis was found after six months' follow-up, and spontaneous recanalisation of both canaliculi occurred. This tumour is believed to be a primary adenosquamous carcinoma of the caruncle and possibly the first reported case. Long term follow up is planned to detect late metastasis, but complete excision of the tumour and its favourable site should yield a good prognosis.

A 76-year-old Caucasian woman presented with a painless swelling in the inner corner of her right eye. This had been slowly growing over a period of several months. On examination, a firm round swelling with an ulcerated top was present in the area of the right caruncle, measuring 2×2 cm in diameter (Fig. 1). On biomicroscopy the lesion appeared to compress both the lacrimal canaliculi. The patient, however, did not complain of epiphora. No regional lymphadenopathy was present. Further ocular examination, the medical history, and physical examination provided no additional information.

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Complete excision of the swelling was performed two weeks later. This necessitated the excision of parts of both lacrimal canaliculi, but no reparative surgery was performed at that time. Postoperative recovery was uneventful, with good cosmetic results (Fig. 2).

PATHOLOGICAL FINDINGS

A white, ovoid, fleshy mass about 1·0 cm in maximum dimension was partly covered by skin and with fat attached to the deep margin. Microscopic examination showed the mass to consist of a carcinoma arranged in sheets and trabeculae (Fig. 3). There were interconnected small cystic spaces in the

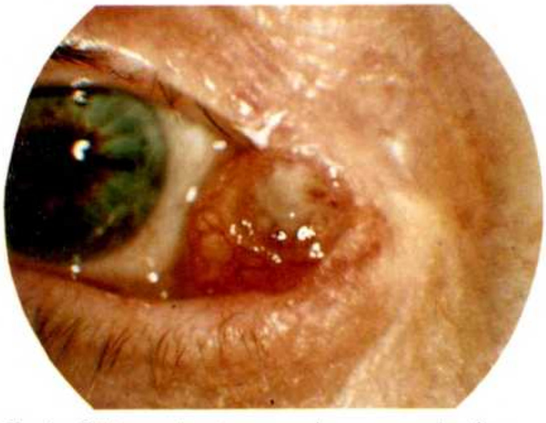

Fig. 1 *Right eye, showing a round mass occupying the region of the caruncle.*

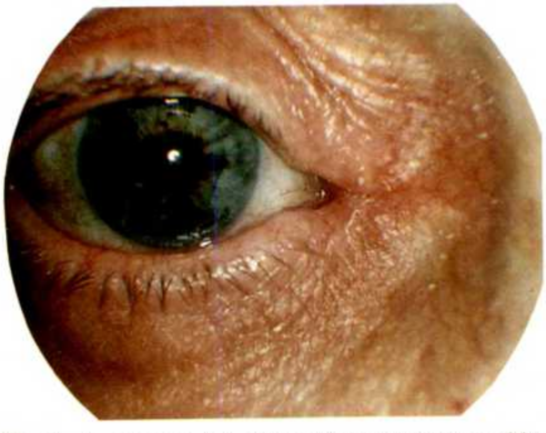

Fig. 2 *Appearance of the right eye following excision of the tumour. No evidence of epiphora.*

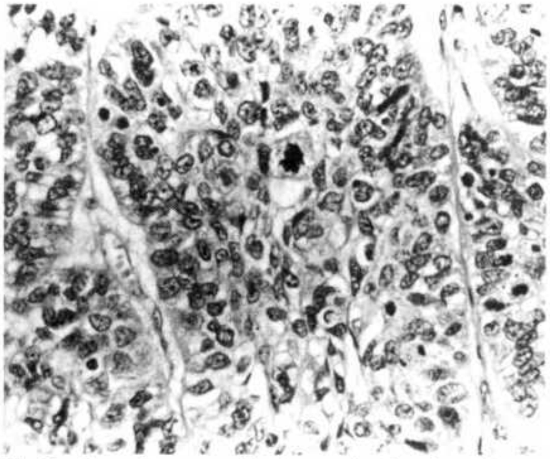

Fig. 3 *Caruncle arranged in sheets and trabeculae with occasional mitosis. (Haematoxylin and eosin, × 234).*

centre of the tumour and a possible punctum opening on to normal skin covering the surface (Fig. 4). The deep margin had a fairly well defined and rounded border with a fibrous pseudocapsule (Fig. 5) in which were a few chronic inflammatory cells. The appearance suggested that the tumour had arisen in a gland opening into the skin surface.

The tumour was composed mainly of clear cells with moderate nuclear pleomorphism and a moderate number of mitoses. In some places there was partial glandular differentiation and in others squamous changes (Fig. 6). Stains for mucins were negative, and there was only a little glycogen. Classification proved difficult, but descriptively it was an 'adenosquamous' carcinoma probably arising in glands of the caruncle.

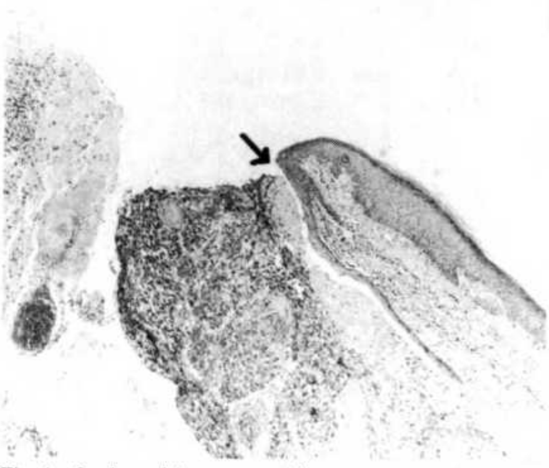

Fig. 4 *Surface of the tumour with a punctum opening on to the skin (arrowed). (Haematoxylin and eosin, × 40.)*

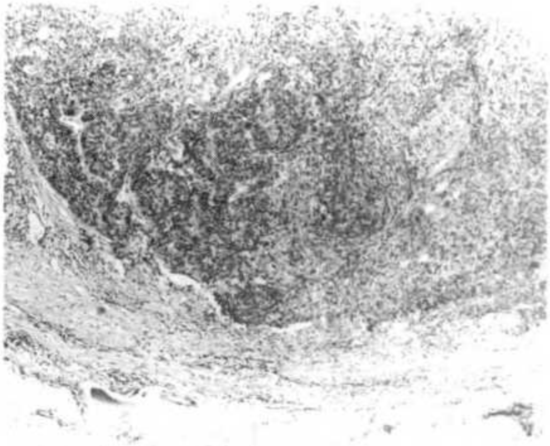

Fig. 5 *Subcutaneous border of the tumour with fibrous pseudocapsule in the lower part of the picture. (Haematoxylin and eosin, × 40.)*

FOLLOW-UP

In view of the pathological findings the patient was fully investigated to exclude the presence of systemic malignancy. Full physical examination, chest x-ray, full blood count, and liver function tests showed no abnormality. A six-month follow-up showed no

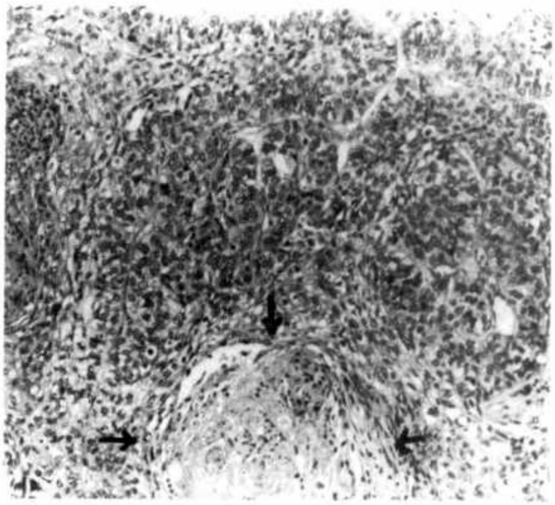

Fig. 6 *There is trabecular carcinoma in the upper part with occasional acinar spaces. The lower centre shows keratinising tumour (arrowed). (Haematoxylin and eosin, × 105.)*

evidence of systemic malignancy and no local recurrence of tumour. The lacrimal canaliculi remained patent, and the patient did not complain of epiphora.

Discussion

Caruncle tumours are relatively rare,[1-3] and malignant tumours are reported to be extremely rare in this region.[2] The commonest tumour is the papilloma,[2,4,5] while sebaceous carcinoma is the commonest malignant tumour.[2]

The caruncle may be the seat of any tumour that occurs in the conjunctiva as well as the adjacent skin of the eyelids. This is because embryologically the caruncle is developed from the lower eyelid, being cordoned off by the lower canaliculus.[6] Although the surface epithelium is mucous membrane, the caruncle bears all the skin elements, including hair follicles, sweat glands, and sebaceous glands.[7]

We were unable to find any previous reports of mixed adenosquamous carcinoma arising within the caruncle region, and it is our belief that this is the first reported case. Cases of adenocarcinoma and squamous carcinoma in the caruncle have been reported[8,9] but not mixed. Luthra *et al.*[1] in reviewing 112 caruncle lesions found no such lesion. Ni *et al.*[10] studied 512 cases of malignant eyelid tumours and found no similar lesion.

The possibility of this tumour being metastatic in origin was raised. However, no systemic malignancy was found after a six-month follow-up. The possible routes of spread of caruncle tumour should be considered. Apart from the usual routes of spread, namely, blood stream, lymph vessels, and direct metastases, Kielar[11] has suggested the possibility of intracanalicular shedding of the tumour cells as an additional route. In the present case both canaliculi appeared to be involved, and complete excision of the tumour involved part of the canaliculi. Of interest, however, is the full recanalisation of both canaliculi and absence of epiphora following surgery.

The possibility of metastases is still present. Luthra *et al.*[1] reported a case of sebaceous gland adenocarcinoma that first recurred 10 years after excision followed by a second recurrence a year later, then a third recurrence the following year. This was in spite of surgery and irradiation therapy. Wilkerson and Winguist[12] reported a bilateral papillary cystadenoma occurring in a woman six months after the first appearance.

In our case we believe the early detection and radical excision of the tumour may yield a better prognosis for the patient. It is generally believed that their relative isolation, ease of removal, and early detection and treatment usually result in an increased survival.[10,13]

We thank Mr J M Smail for allowing us to describe this case; P W Leedham for reporting on the histology; and Sue Fraser for typing this paper.

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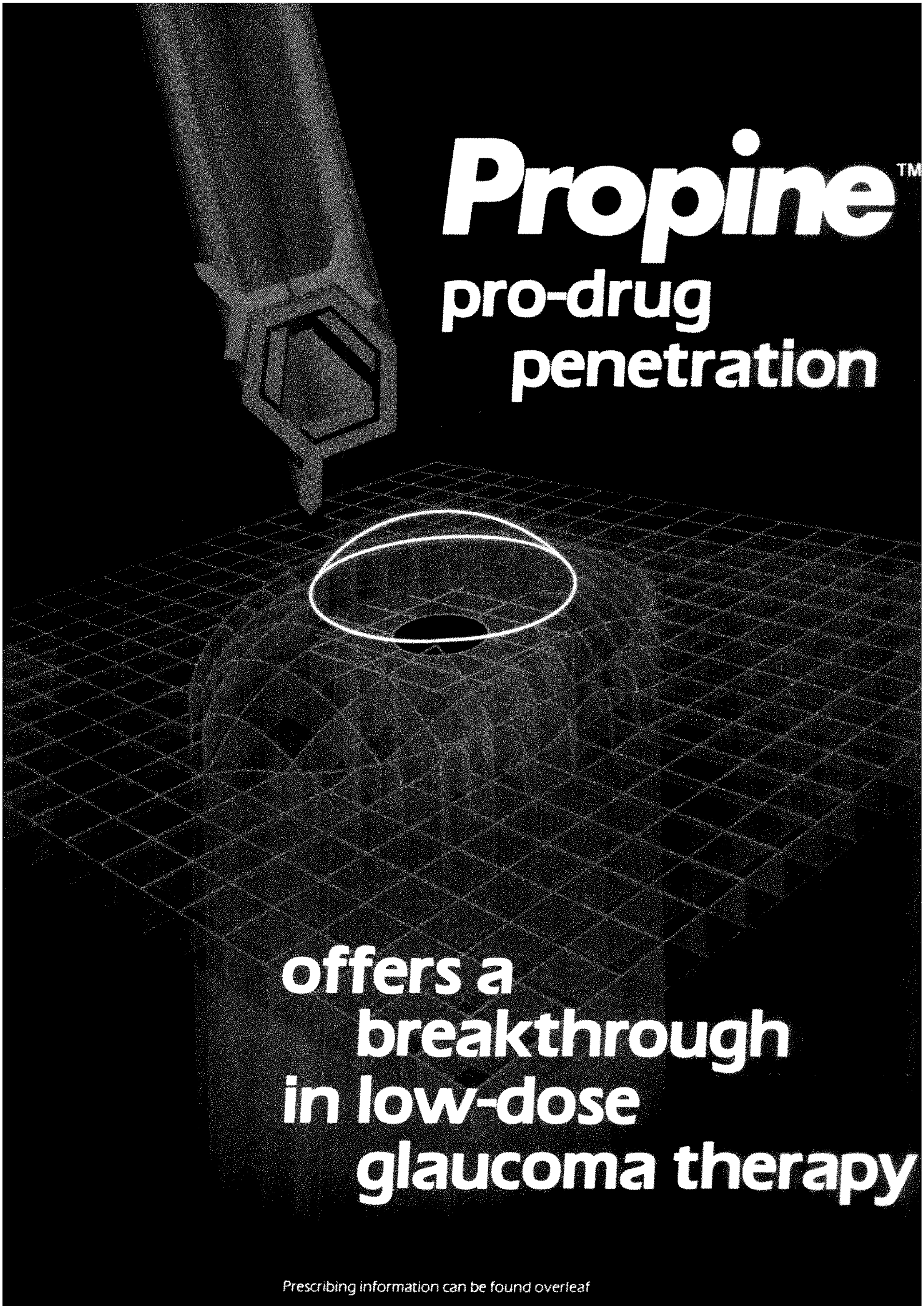

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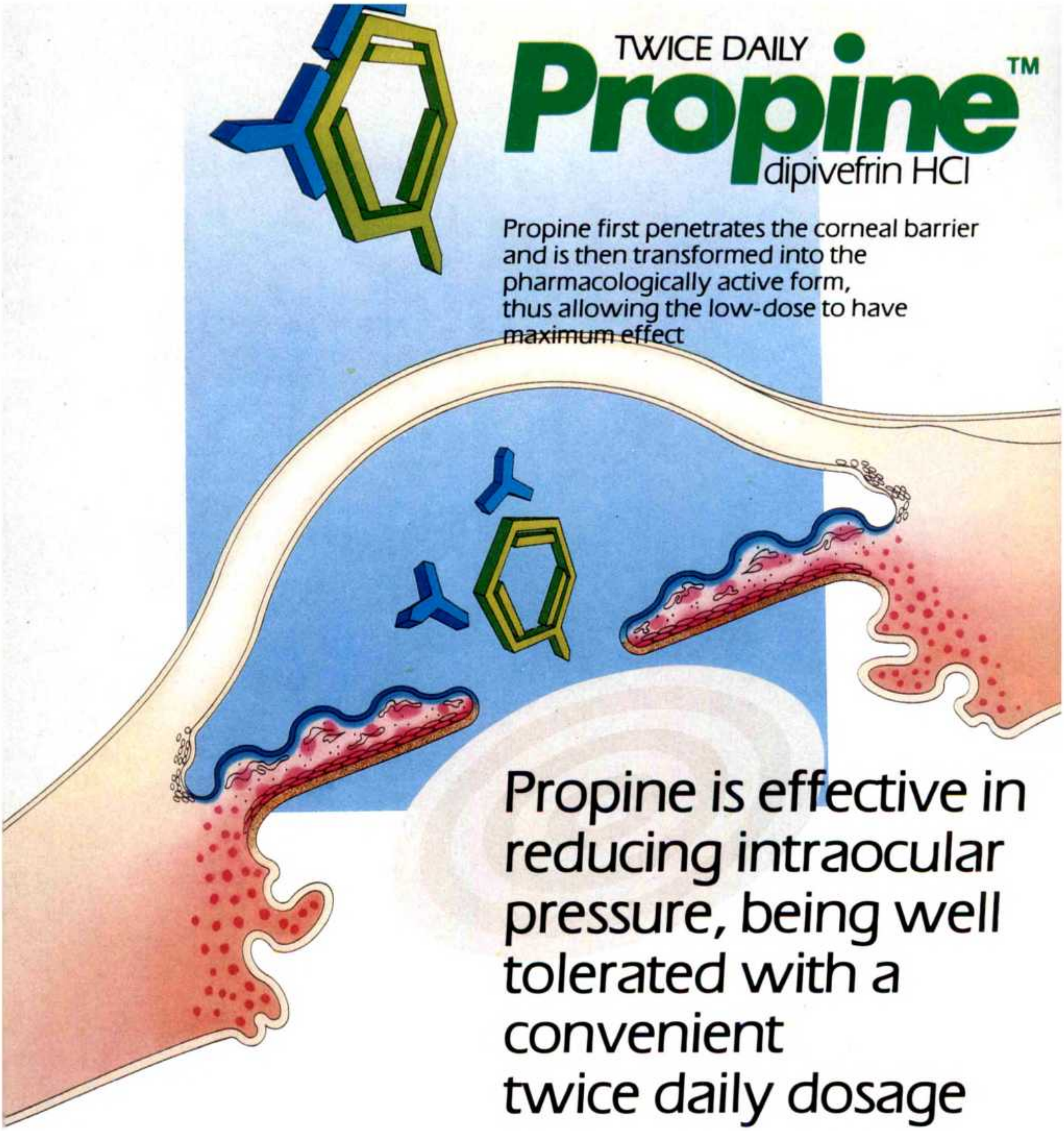

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British Journal of Ophthalmology, 1986, **70**, 867–868

Diverticulum of the lacrimal sac associated with rhinosporidiosis

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SUMMARY A rare case of diverticulum of the lacrimal sac associated with rhinosporidiosis is reported. The clinical presentation and possible pathogenesis are discussed.

Diverticulum of the lacrimal sac of sufficient size to cause clinical symptoms is rare.[1] It may be of congenital, inflammatory, or traumatic origin. Mycotic dacryocystitis due to rhinosporidiosis has been noted.[2] Blastomycosis of the nasolacrimal duct associated with diverticulum of the lacrimal sac has been observed.[3] In the present case diverticulum of the lacrimal sac associated with rhinosporidiosis is being reported.

Case report

A South Indian female aged 19 years was admitted to the Department of Ophthalmology on 28 December 1984 complaining of a swelling at the right inner canthus of three years' duration. The swelling was gradually increasing along the right lower lid. There had been epiphora with occasional blood stained discharge for the past three months.

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On examination there was a soft swelling extending from the medial canthus to the medial two-thirds of right lower orbital margin (Fig. 1). It was painless, and the surface was smooth and slippery, adherent to neither overlying skin nor underlying bone. On pressure a serosanguineous discharge came through both puncta, resulting in shrinkage of the swelling. The left eye showed no abnormality. The ears, nose, and throat were normal.

Syringing the right lacrimal passages after evacuating the discharge resulted in a tense cystic swelling with excruciating pain. The left nasolacrimal duct was patent. Dacryocystography with propyliodine (Dionosil) dye showed a diverticulum of the lacrimal sac and dye did not appear in the nose after 30 minutes (Fig. 2).

A diagnosis of diverticulum of the lacrimal sac was

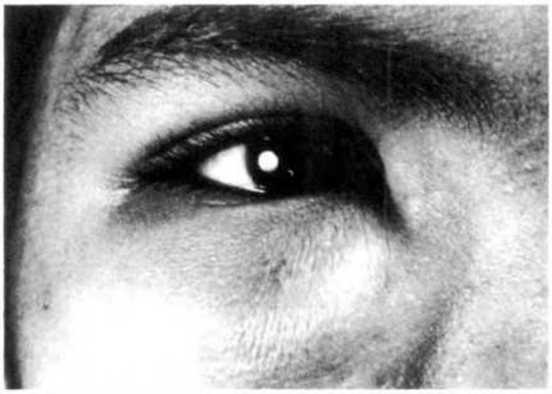

Fig. 1 *Swelling of the medial canthus and the lower lid.*

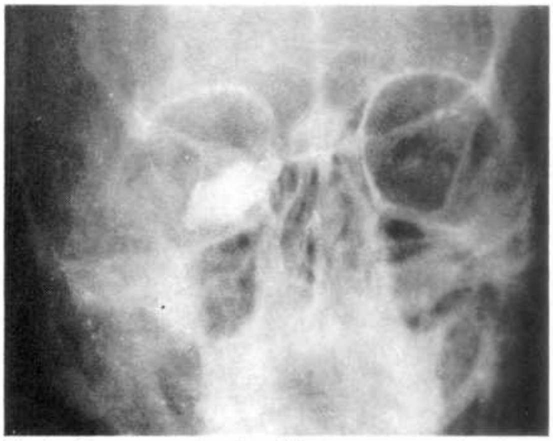

Fig. 2 *Posteroanterior view of dacryocystogram showing diverticulum of the lacrimal sac.*

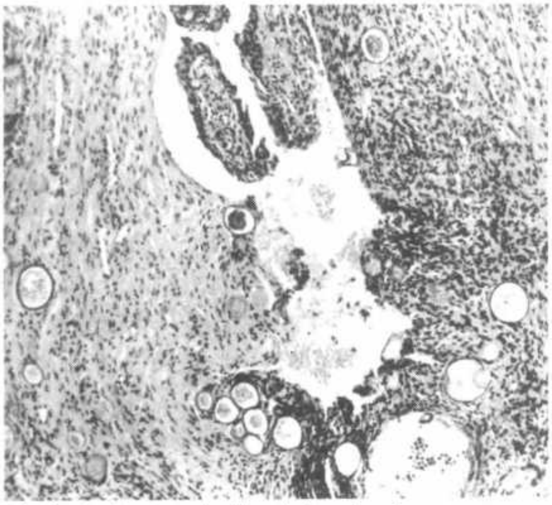

Fig. 3 *Section from the diverticulum showing* Rhinosporidium seeberi *trophocytes and sporangia. (H and E, × 63).*

made, and both diverticulum and sac were excised. Histopathological examination showed thick double walled trophocytes and sporangia of *Rhinosporidium seeberi* in the fibrous tissue of the sac and diverticulum (Fig. 3). Rupture of some of the sporangia had resulted in the release of spores into the wall, producing a giant cell reaction. In addition the sections showed lymphocytic and plasma cell infiltration.

Discussion

Rhinosporidiosis is a fungal infection caused by *Rhinosporidium seeberi*. Oculosporidiosis involves the lacrimal sac in 24% of cases, and a history of bleeding from the nose is often given.[4]

Diverticulum of the lacrimal sac is rare and may be of congenital, inflammatory, or traumatic origin. Either it may be in direct and free communication with the sac or the two structures may be separate.[2] Congenital diverticula have been seen in association with obstruction of the nasolacrimal duct.[5] and an intermittent obstruction of its drainage by vascular engorgements or chronic inflammation.[1] Diverticulum accompanied by an infection of the nasolacrimal duct by blastomycosis[3] and recurrent lacrimal abscess with patency of the nasolacrimal passages[6] have been reported. Trauma, for instance from rough, repeated probings, may also result in a diverticulum.[5]

The development of the diverticula of the lacrimal sac cannot be explained solely by mechanical factors. The changes are usually congenital malformations.[5] In the present case probably the following sequence of events occurred. There may have been a symptomless congenital diverticulum of the lacrimal sac with patency of passages. Rhinosporidiosis of the lacrimal passages caused intermittent obstruction by chronic inflammation and venous engorgement, resulting in retention of secretion, which presented clinically as an obvious swelling, epiphora, and blood stained discharge.

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A recent epidemic of Coxsackie virus type A24 acute haemorrhagic conjunctivitis in Singapore

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SUMMARY A recent epidemic of acute conjunctivitis in Singapore showed again the importance of Coxsackie virus type A24 variant as a causative agent of acute haemorrhagic conjunctivitis (AHC). Although the ocular manifestations appeared similar to those described for the 1970 and 1975 outbreaks, a markedly higher rate of respiratory involvements was noted. Not observed in previous epidemics were herpes-like vesicles in the conjunctiva and eyelids of one patient and vesicles in the buccal mucosa and lips of another from whom Coxsackie virus A24 was isolated. The most interesting finding in this study was the isolation of five wild (non-Sabin) poliovirus type 1 strains. Three strains were obtained from conjunctival and two from throat swabs of patients with mild to severe conjunctivitis. It is conceivable that the rare reports of polio-like paralysis or radiculomyelitis accompanying or following AHC in a few Asian countries could be attributed to concurrent infections with a poliovirus and either enterovirus type 70 or Coxsackie virus type A24.

Acute haemorrhagic conjunctivitis (AHC), known also as Apollo II disease, Singapore epidemic conjunctivitis, picornavirus epidemic conjunctivitis, and Bangla Joy conjunctivitis has affected hundreds of millions of people since its appearance in Ghana, Africa, in June 1969, where the first clinical description was given.[1] The conjunctivitis swept rapidly along the coastal areas of West, East, and North Africa to major cities in the Indian subcontinent, Southeast Asian countries including Japan, and a few European countries in 1970 and 1971.[2] Large epidemics were confined to the eastern hemisphere, where crowding and unhygienic living conditions contributed to spread of the disease. The first outbreak in the western hemisphere was in the Americas (Brazil) in mid 1981.[3] At the time of writing the only continent apparently spared this unusually contagious eye affliction was Australia.

Two picornaviruses, namely, a new Coxsackie virus type A24 (CA24) variant isolated for the first time during the 1970 epidemic of acute conjunctivitis in Singapore[4-7] and a new enterovirus—enterovirus type 70 (EV70) isolated from similar epidemics in Morocco, Singapore, and Japan in 1971.[8-11]—are now universally recognised as causative agents of AHC. The first epidemic of CA24 was in August 1970 and the second in June 1975.[12] EV70 was responsible for epidemics in June 1971,[8-11] August 1978,[13] and July 1980.[14] In all instances outbreaks caused by CA24 variant were more explosive and extensive than those caused by EV70. However, the types of conjunctivitis caused by these two picornaviruses are indistinguisable.

The common features of AHC are mild to severe follicular conjunctivitis, subconjunctival haemorrhage in severe cases, which gave it the name 'acute haemorrhagic conjunctivitis,' and fine pinpoint epithelial keratitis. Punctate subepithelial keratitis and corneal erosion are rare. The conjunctivitis generally resolved within one to two weeks of onset without sequalae. Respiratory and gastrointestinal disturbances accompany some cases. Secondary bacterial infections are common.[4-8] Rare cases of neurological complications including radiculomyelitis, palatal paresis, and Bell's palsy accompanying or following conjunctivitis caused by EV70 have been reported from India, Taiwan, Thailand, and America.[15-20]

We present here the clinical and laboratory findings of the March–June 1985 epidemic of acute conjunctivitis in Singapore. For the 12-week period a total of 29 920 patients were treated by Government

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clinics (Tan J L personal communication).[1] This is the third major outbreak of AHC caused by the CA24 variant in Singapore.

Materials and methods

Clinical investigation. A random study was carried out on 65 patients who attended the Government Clementi Polyclinic. The patients ranged from 3 to 55 years old. All these patients sought treatment within the first three days of the onset of conjunctivitis with the exception of three, one of whom was examined on the fourth day, one on the fifth, and one on the seventh day. Conjunctival swabs, tears, throat swabs, and blood where agreed to by the patients were collected and tested by the methods described[4 5 12 21]

Virus isolation and identification. Conjunctival and throat swabs were processed and inoculated into HeLa cell cultures grown in microtitration plates, and virus isolates were identified by a microneutralisation test with monkey antisera to CA24 (Singapore Epidemic Conjunctivitis 1970) virus and EV70 (Singapore Epidemic Conjunctivitis 1971) as described.[21 22] Tear samples were examined for virus particles by electron microscopy.[22]

Serology. Each sample of serum was tested for antibody to both CA24 virus and EV70 by a microneutralisation test.[22]

Results

Table 1 presents an analysis of the 65 patients studied. More females than males were affected, with a preponderance in the 5 to 14 and 15–24 year age groups.

Bilateral conjunctivitis was present in 43 (66·2%), lid swelling in 45 (69·2%), mild conjunctivitis in 29 (44·6%), severe conjunctivitis in 36 (55·4%), and purulent discharge in 12 (18·5%). Subconjunctival haemorrhage was seen in 14 (21·5%) patients, one of whom had corneal oedema. Herpes-like vesicles were seen in the conjunctiva and skin of the eyelids of one patient.

Upper respiratory tract infections were seen in 54 (83·0%) cases, and in 1 (1·5%) patient vesicular lesions in the buccal mucosa and lips. Twenty-two (33·8%) patients complained of headaches, 7 (10·8%) of gastrointestinal disturbances, and 1 (1·5%) of anorexia with myalgia.

From 61 conjunctival swabs 51 strains of CA24 virus and three strains of poliovirus type 1 were isolated. Forty-nine strains of CA24 virus, and two of poliovirus type 1 were recovered from 63 throat swabs. Seven of 11 tear samples (63·6%) contained virus particles resembling picornaviruses.

Table 1 *Analysis of 65 cases of acute conjunctivitis (1985)*

	Number of cases	*Percentage*
Age 0–4	2	3·0
5–14	23	35·4
15–24	17	26·2
25–34	11	16·9
35–44	8	12·3
45–54	3	4·6
55–64	1	1·5
Male	26	40·0
Female	39	60·0
Laterality		
Bilateral	43	66·2
Unilateral	22	33·9
Conjunctivitis		
Mild	29	44·6
Severe	36	55·4
Subconjunctival haemorrhage	14	21·5
Corneal oedema	1	1·5
Vesicles in conjunctiva and eye lid	1	1·5
Lid swelling	45	69·2
Purulent discharge	12	18·5
Coryza	24	36·9
Pharyngitis	54	83·0
Tonsillitis	2	3·1
Cough	7	10·8
Vesicles in buccal mucosa and lips	1	1·5
Headache	22	33·8
Anorexia and myalgia	1	1·5
Gastrointestinal disturbances	7	10·8

Only one of 16 patients from the study series donated a second blood sample. A four-fold neutralising antibody (NA) rise from 20 to 80 to CA24 virus was registered between the acute and convalescent sera in this patient. Fourteen of 16 acute sera (87·5%) had no (<20) NA to CA24 virus, while the remaining two had titres of 20 and 80 respectively. Eight of these 16 acute sera had no (<20) NA to E70, five a titre of 20, two a titre of 40, and one a titre of 80.

Twenty-eight patients had had previous attack of the conjunctivitis: nine in 1984, eight in 1983, two in 1982, three in 1980, and one each in 1978, 1975, 1973, 1970, and 1981/1982; and one patient complained of yearly episodes of conjunctivitis.

Discussion

The third extensive epidemic of acute conjunctivitis caused by CA24 in April–June 1985 resembled the previous two epidemics in August 1970 and June 1975. The manifestations of conjunctivitis were similar to those described.[4 8 12] The striking features of severe acute haemorrhagic conjunctivitis are shown in Fig. 1 to 3 taken of a 12-year-old boy one week after the onset of conjunctivitis. Blood stained tears, severe ecchymoses and subconjunctival haemorrhage, follicular hypertrophy of palpebral conjunctiva, and ptosis are seen.

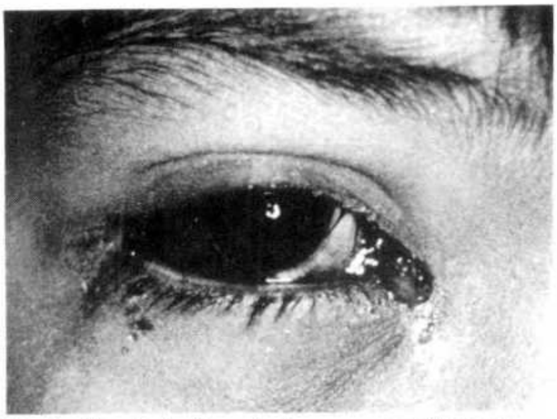

Fig. 1 *Blood stained tear discharge, severe ecchymoses, subconjunctival haemorrhage, and ptosis.*

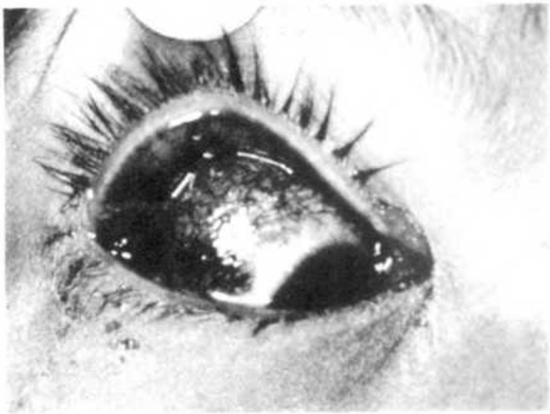

Fig. 2 *Follicular hypertrophy of palpebral conjunctiva and blotches of subconjunctival haemorrhage.*

Most patients (83%) had respiratory tract infections and many (33·8%) complained of headaches. Not observed before was the presence of herpes-like vesicular lesions in the conjunctiva and skin of the eyelids of one patient and in the buccal mucosa and lips of another from whom CA24 virus was isolated.

Interestingly, of 54 isolates obtained from 61 conjunctival swabs 51 were CA24 virus and three poliovirus type 1. Forty-nine of 51 isolates from 63 throat swabs were of CA24 virus and two of poliovirus type 1. Of the five poliovirus isolates two were from the throat of a 9-year-old boy and an 8-year-old girl whose conjunctival swabs yielded CA24 virus. One came from the conjunctival swab of a 30-year-old woman whose throat swab yielded a CA24 virus, and the remaining two poliovirus strains were from the conjunctival swabs of women age 27 and 30 years whose throat swabs were virus negative. Intratypic serodifferentiation by the enzyme-linked immunosorbent assay with strain specific antisera showed these poliovirus type 1 strains to be wild (non-Sabin) poliovirus strains.

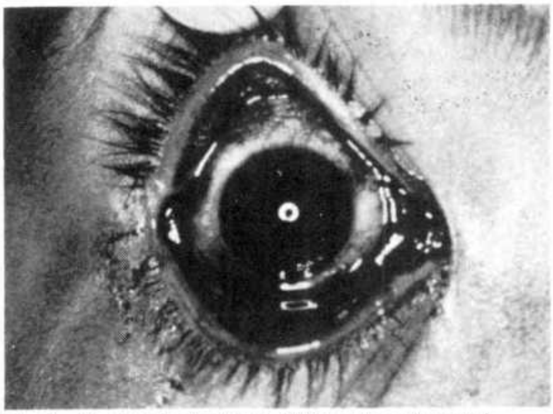

Fig. 3 *Conjunctival oedema, diffuse subconjunctival haemorrhage. No membrane formation, and cornea is clear.*

This is not the first time that poliovirus strains have been isolated from the conjunctiva of patients during epidemics of acute haemorrhagic conjunctivitis. Two virus strains from conjunctival swabs obtained during the 1971 and one from the 1975 conjunctivitis epidemics in Calcutta sent to us by Professor J K Sarkar, Department of Virology, School of Tropical Medicine, were identified as poliovirus type 1. This finding was confirmed by Dr R Kono, Central Virus Diagnostic Laboratory, Tokyo, Japan, who received duplicate aliquots of these isolates. Furthermore, an isolate from a conjunctival swab sampled during the 1984 epidemic in Malaysia caused by EV70 received from Dr S K Tan, Institute of Medical Research, Kuala Lumpur, was identified as poliovirus type 2. The poliovirus type 1 and poliovirus type 2 strains were also forwarded by us to Dr Van Wezel, and they were typed as non-Sabin poliovirus type 1 and type 2 respectively. In all these instances the laboratories were not involved in poliovirus investigation during the AHC epidemics.

It is conceivable that rare cases of polio-like paralysis following AHC reported in a few Asian countries may be due to concurrent infections with a poliovirus and an EV70 or CA24 virus.

It is not surprising that only two of 16 acute sera contained neutralising antibody to CA24 in view of the fact that the last epidemic of CA24 AHC occurred in 1975. The higher number (eight out of 16) seropositive for EV70 could be accounted for by the more frequent and recent E70 outbreaks in 1971, 1978, 1980, and the last quarter of 1983 to beginning of 1984. Sporadic cases of EV70 were observed together with CA24, adenovirus types 3, 7, 8, 11, and 19 during interepidemic periods.

Rapid and early diagnosis of AHC can be achieved by electron microscopy if the infecting agents are sufficiently abundant in tears during the early onset of conjunctivitis. Seven of 11 tear samples contained picornavirus-like particles. CA24 cannot, however, be distinguished from E70 morphologically, but these AHC viruses can be differentiated from adenovirus serotypes, which give rise to conjunctivitis clinically similar to that caused by CA24 and E70.[23-25] Although isolation in tissue cell cultures is more sensitive than electron microscopy for the detection of CA24, it requires several days for cytopathogenic effects to appear, and in the case of E70 several tissue culture passages are required. A reliable isolation system for E70 has yet to be found, and often diagnosis depends on serological tests.

Twenty-eight of 65 patients recalled a previous attack of conjunctivitis, 18 within the past two years, including one who complained of yearly attack for many years.

The frequent involvement of the CA24 variant in epidemics of acute haemorrhagic conjunctivitis and the extremely contagious nature of this eye infection is clearly shown by the explosive and extensive outbreaks in Singapore,[4-6] Malaysia, and Hong Kong in 1970;[5] Singapore,[12] Hong Kong,[26] Bombay and Poona,[27] New Delhi,[28] Bangladesh (Thongcharoen P, personal communication), Sri Lanka,[29] Brunei,[30] Bangkok,[31] and Vellore[32] in 1975; Malaysia[33] and Sri Lanka (Vitaran T, personal communication) in 1978; Poona, (Pavri K M, personal communication), Bombay,[34] and Vellore in 1979.[35] Our investigation of the current epidemics of AHC in Brunei which started in August and in Malaysia in December 1985 shows they also are of CA24 virus aetiology.

The epidemicity and pandemicity of enterovirus conjunctivitis is said to be parallelled by only one other viral disease—influenza.

We thank Dr Ng Yook Kim, Medical Director of Outpatient Services, Primary Health Care Services, Ministry of Health, Dr Lim Gek Nee, Registrar of Maternal Child Health Services, and Madam Chew Kim Boon, Nursing Officer of the Clementi Polyclinic for having made it possible for us to carry out this study. We are also grateful to Dr A L van Wezel, Rijks Instituut voor Volksgezonheid en Milieuhygiene, The Netherlands, for intratypic serodifferentiation of the poliovirus strains, to Mrs Josephine Howe for assistance in photography, and to the Singapore Turf Club for financial support.

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British Journal of Ophthalmology, 1986, **70**, 874

Correspondence

Retinal detachment

SIR, I read with interest the article by Ho and Tolentino.[1] The probable causal element of the 14 detachments reported post capsulotomy is not emphasised in this article. It would be nice to know how and when the posterior capsulotomies were done in relation to the retinal detachments. As others have reported, and our experience supports, neodymium: YAG laser posterior capsulotomy can be associated with rhegmatogenous retinal detachment.[2]

In response to the authors' statement in the concluding paragraph, ECCE (and PC-IOL) probably does minimise the incidence of postoperative retinal detachment, but posterior capsulotomy probably increases the likelihood of same.

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SIR, Extracapsular cataract extraction (ECCE) and posterior chamber intraocular lens (PCIOL) implantation are becoming the procedure of choice among cataract surgeons. Many surgeons performing this type of surgery on a regular basis would share the same concern and interest with Dr Hall about the causal relationship of posterior capsulotomy and retinal detachment.

As stated in our article,[1] we were not the primary surgeons for any of the capsulotomy operations, and the nature of a retinal referral practice made it difficult to obtain details of the circumstances surrounding the capsulotomies in all 14 cases in our report. However, in four of six cases (case 3, 7, 10, and 11), the retinal detachment was detected within two weeks of the posterior capsulotomy. The temporal relationship in these cases would lead one to suspect that the detachment might have been precipitated by the capsulotomy. Furthermore, in cases 10 and 11 vitreous gel was observed to herniate anteriorly through the capsulotomy around the IOL into the anterior chamber. Although the preoperative finding of vitreous gel in the anterior chamber in front of the IOL has been reported to be associated with a poor prognosis,[2] the retinal detachments in both of these cases were successfully repaired.

The pathogenetic mechanism of pseudophakic retinal detachment following posterior capsulotomy is still uncertain. In the two cases where there was forward movement of the vitreous gel into the anterior chamber one might speculate that the anterior displacement of the vitreous mass would increase peripheral vitreous traction on the vitreous base resulting in retinal breaks.[3,4] But in the majority of our cases, and as observed by others,[5] the absence of anterior movement of the vitreous in front of the iris plane would suggest an alternative mechanism for the detachment. It is generally difficult to separate visually the anterior hyaloid face from the opacified posterior capsule under the operating microscope or the slit-lamp biomicroscope. Consequently, the anterior hyaloid face is frequently violated during the posterior capsulotomy procedure. It is possible that the broken anterior hyaloid surface allows anterior movement of proteins and macromolecules from the vitreous gel, resulting in fluid shifting within an already syneretic vitreous cavity, leading to increased peripheral retinal traction and break formation. Even with an intact anterior hyaloid surface a rent in the posterior capsule disrupts the physical barrier between the anterior and posterior segments of the eye similar to that of the aphakic eye after intracapsular lens extraction. The loss of this barrier may facilitate diffusion of hyaluronic acid, a stabiliser of the vitreous gel, into the anterior chamber,[3,6] and this situation is manifest clinically as collapse of the vitreous gel.[7]

We share Dr Hall's impression that ECCE and PCIOL probably minimise the incidence of postoperative retinal detachment, and posterior capsulotomy probably increases the likelihood of same. We await a well conducted prospective study to confirm our suspicion.

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Treatment of retinal detachment

SIR, I have read with interest Gilbert and McLeod's[1] paper on the preliminary drainage of subretinal fluid in the treatment of retinal detachment. Just for the record, and for further information of those primarily concerned with retinal surgery, I wish to point out that the indications, advantages, complications, and technique of that procedure have been extensively dealt with by me in a previous report.[2]

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Sir, Your correspondent rightly draws attention to his excellent paper describing the merits of preliminary drainage of subretinal fluid, followed by intravitreal saline injection, in the management of bullous retinal detachments. However, the main purpose of the paper on D-ACE surgical sequence was to popularise preliminary fluid drainage in the context of the use of intravitreal air tamponade (which thus achieves initial break-closure and allows low-profile scleral buckling to be employed for subsequent maintenance of break-closure). Whenever intravitreal injection is contemplated in order to restore ocular volume after drainage of subretinal fluid, I would submit that there are few instances wherein fluid injection is to be preferred over air injection, thus denying the patient the benefits of internal break tamponade.

As I have recently discovered, details of D-ACE surgical sequence are also to be found in Schepens' textbook.[1]

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Reference

1 Schepens CL. 'Second method' for treatment of fishmouth breaks. *Retinal detachment and allied diseases*. Philadelphia: Saunders, 1983; **2:** 505.

Gonococcal conjunctivitis

Sir, Gonococcal infection is a potentially blinding disease in African adults as shown by Schwab and Tizazu.[1] These authors describe an epidemic of gonococcal keratoconjunctivitis that caused severe damage in 23 out of 32 (72%) infected eyes. They should be congratulated for bringing this problem to the attention of the medical community, but unfortunately they fail to recommend an adequate therapeutic approach for gonococcal conjunctivitis in order to prevent eye damage in the future.

In recent years there has been an increase of gonococcal conjunctivitis in adults and neonates in most of sub-Saharan Africa.[2] With the advent of gonococcal strains which are either less sensitive to penicillin (chromosomal resistance) or totally resistant to this antibiotic (penicillinase-producing *Neisseria gonorrhoeae* = PPNG), severe complications are more and more encountered in referral clinics. Partly responsible for this situation are the dispensaries and peripheral health units who continue to treat gonococcal conjunctivitis with topical antibiotics and/or low dose systemic penicillin, despite this problem of resistance. Schwab and Tizazu, who considered this possibility, apparently rejected it based upon their microbiological findings. They reported that five strains tested with disc diffusion were sensitive to penicillin. Microbiological support being far from optimal in developing countries, the strains could not be tested for penicillinase production. The possibility of plasmid resistance (PPNG strains) or chromosomal resistance among a number of their isolates therefore cannot be excluded.

In Rwanda we recently observed several cases of adult gonococcal keratoconjunctivitis comparable to the cases described in Malawi. Since the first description of a PPNG strain in this country in 1982, the prevalence has now risen to 60% in Kigali, the capital.[3] Consequently our standard treatment, following recent WHO recommendations,[4] consists of spectinomycin 2 g or cefotaxime 1 g intramuscularly in a single dose plus 10 days of topical 1% tetracycline ointment. With this treatment conjunctivitis subsides in 24 to 48 hours and progression of complications is immediately aborted. In Malawi some cases went on to severe eye damage although receiving high doses of penicillin, which could be indicative of causative strains resistant to this antibiotic.

Once penicillin resistant strains emerge, a switch in treatment for gonococcal conjunctivitis from penicillin to spectinomycin or one of the newer cephalosporins should be considered. Health authorities and clinicians alike often resist this change, arguing that the large majority of strains remain sensitive to penicillin and that these newer antibiotics are more expensive and less readily available. But in countries which do not have an effective gonorrhoea control programme, once introduced the PNNG strains increase exponentially and two to three years later account for up to 70% of circulating gonococci.[5] The implementation of the new treatment recommendations is then an absolute necessity, otherwise gonococcal conjunctivitis again becomes a blinding disease in those countries.

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Sir, Drs Kestelyn and Meheus correctly point out a few of the difficulties inherent in dealing with a potentially destructive ocular infection in a developing country where medications, manpower, and laboratory support systems are limited.

We were unable to assess the biology of the *Neisseria gonorrhoeae* strains responsible for infections in Malawi. It was not possible in our clinical setting to study chromosomal resistance or PPNG strains because of the unavailability of required supplies in the hospital bacteriological laboratory. Indeed, we knew of the probability of the presence of resistant strains of *Neisseria gonorrhoeae* but could do little else but continue treatment with the only antibiotics available, topical tetracycline and systemic penicillin.

Many eyes in our series which were lost due to endophthalmitis from *Neisseria gonorrhoeae* had already sustained corneal perforation from corneal ulceration at the time the patients were admitted to hospital. Others who presented with severe gonococcal keratoconjunctivitis went on to corneal perforation during hospitalisation despite tetracycline and penicillin treatment, lending credence to the supposition that *Neisseria gonorrhoeae* resistant strains were present. We would have switched our therapy to spectinomycin or one of the newer cephalosporins had any of these drugs been available.

Not only in Rwanda is gonococcal antimicrobial resistance a problem, as Drs Kestelyn and Meheus write, it is also a great concern in Kenya, where penicillinase-producing and beta lactamase plasmid-containing strains complicate therapy.[1] We have documented the periodic problem of epidemic gonococcal keratoconjunctivitis in adults in Malawi by probable, but unproved, penicillinase-producing and plasmid-containing strains. Almost certainly this spectacular epidemic adult blinding infection has occurred in other African nations.

Drs Kestelyn and Meheus have noted the World Health Organisation's treatment recommendations for ocular gonococcal infection. The Centre for Disease Control (CDC) recommends[2] spectinomycin 2·0 g intramuscularly or ceftriaxone 250 mg IM for patients with venereal gonorrhoea which has persisted after one of the non-spectinomycin regimens has failed or for proved PPNG strains, followed by tetracycline 500 mg p.o. q 6 h × 7 days or doxycycline 10 mg p.o. q 12 h × 7 days. Patients who cannot tolerate tetracycline may be treated with spectinomycin 2·0 g IM followed by erythromycin 500 mg p.o. q 6 h × 7 days. For gonococcal ophthalmia in adults the CDC recommends hospitalisation and treatment with aqueous penicillin G, 10 million units intravenously daily for five days. For PPNG infections cefoxitin 1·0 g IV or cefotaxime 500 mg IV q 6 hours daily or ceftriaxone 1·0 g IM daily are recommended. The CDC does not recommend the use of topical ocular antibiotic preparations.

Improved chemotherapy for resistant *Neisseria gonorrhoeae* offers hope for preventing ocular destruction and blindness in patients with advanced infection. Until governments and international health agencies are able to improve health care systems and provide sufficient and appropriate pharmaceuticals for developing nations, however, destructive gonococcal keratoconjunctivitis will probably increase and will become a more significant cause of irreversible blindness.

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Book review

Parsons' Diseases of the Eye. 17th edn. By STEPHEN J. H. MILLER.. Pp. 384. £19·50. Churchill Livingstone: Edinburgh. 1984.

The seventeenth edition of this well-known text book, produced under the guidance of Sir Stephen Miller, is a worthy successor to previous editions. Perfection is, of course, impossible in a book of this type, attempting as it does to describe far more than is implied in its somewhat modest title. There is indeed a section entitled 'Diseases of the eye,' but there are seven others, covering anatomy and physiology, optics, examination and therapeutics, disorders of motility, diseases of the adnexa of the eye, symptomatic diseases of the eye, and preventive ophthalmology.

When one considers that some major textbooks require between 10 and 20 sizeable volumes to cover the same ground, one realises what a difficult task, both in selection and compression, the author of a single ophthalmological textbook has. The danger with a book of this sort is that it falls between two stools: it may be too complex for the undergraduate medical student or general practitioner but too condensed for the practising ophthalmologist. This book, however, and this paperback edition in particular, is aimed specifically at the student. One takes that to mean the postgraduate beginning a career in ophthalmology; usually in the first years of an ophthalmic residency. It will also be useful to certain general practitioners, practising in remote places, who have to be relatively self-sufficient in basic ophthalmology.

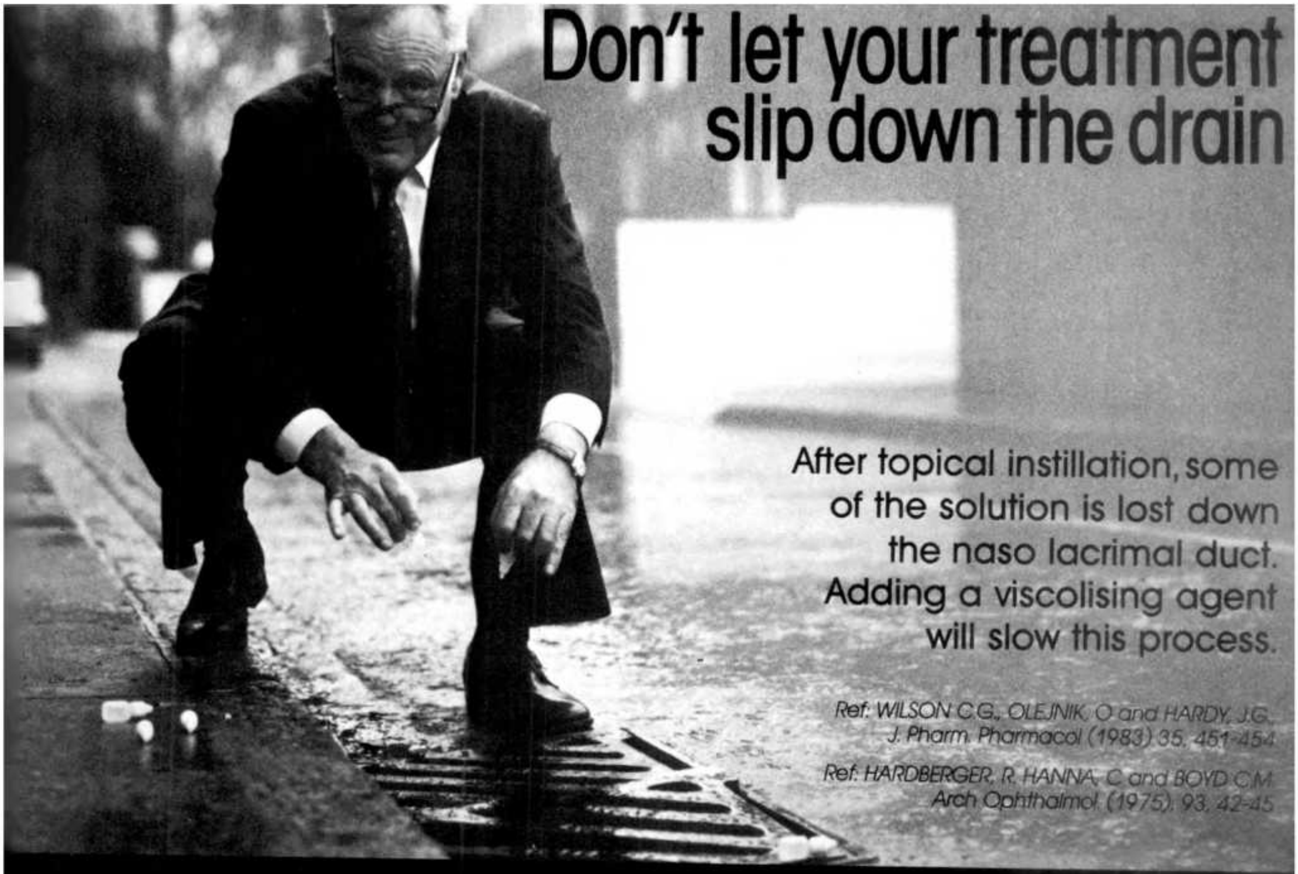
This is a valuable addition to the venerable line of editions of 'Parson's.' The text is clear and eminently readable and the numerous line illustrations from our foremost ophthalmic illustrator blend well with excellent photographs of macroscopic and microscopic subjects.

REDMOND J H SMITH

Note

Cataract

The New Orleans Academy of Ophthalmology will hold its 36th Annual Symposium on 'Cataract in the Nineties' on 14–17 February 1987 at the Hyatt Regency Hotel, New Orleans. Details from Emily Busby (Executive Secretary), New Orleans Academy of Ophthalmology, Eye, Ear, Nose & Throat Hospital, 145 Elk Place, Room 203, New Orleans, LA 70112, USA.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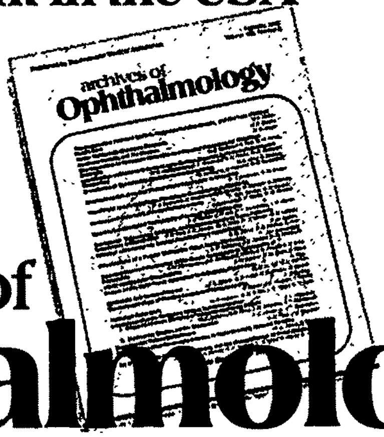

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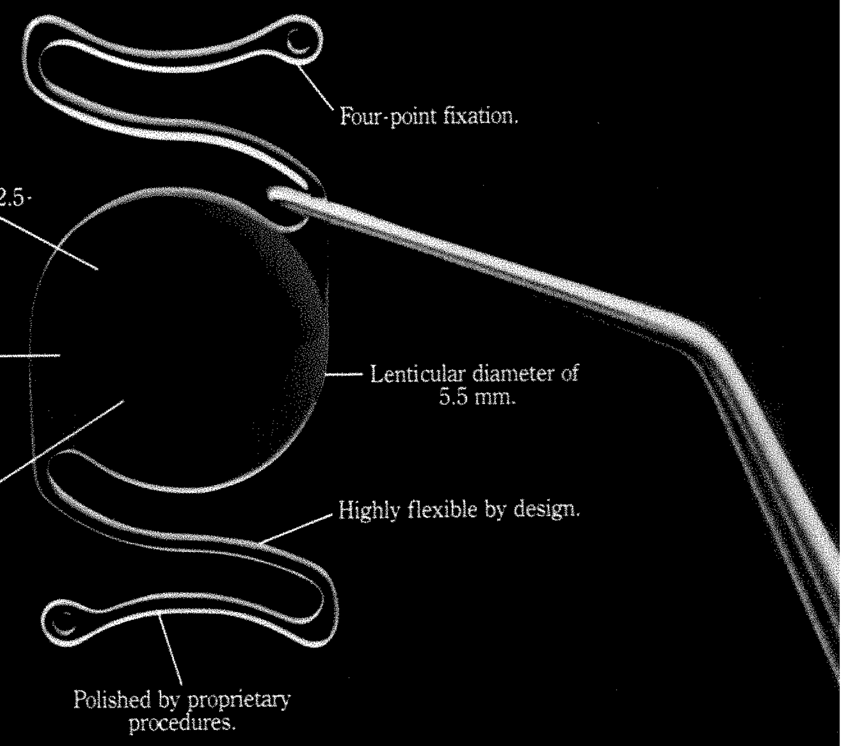
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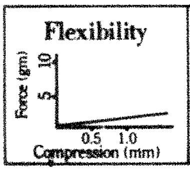

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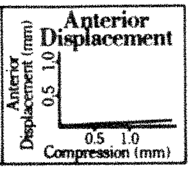

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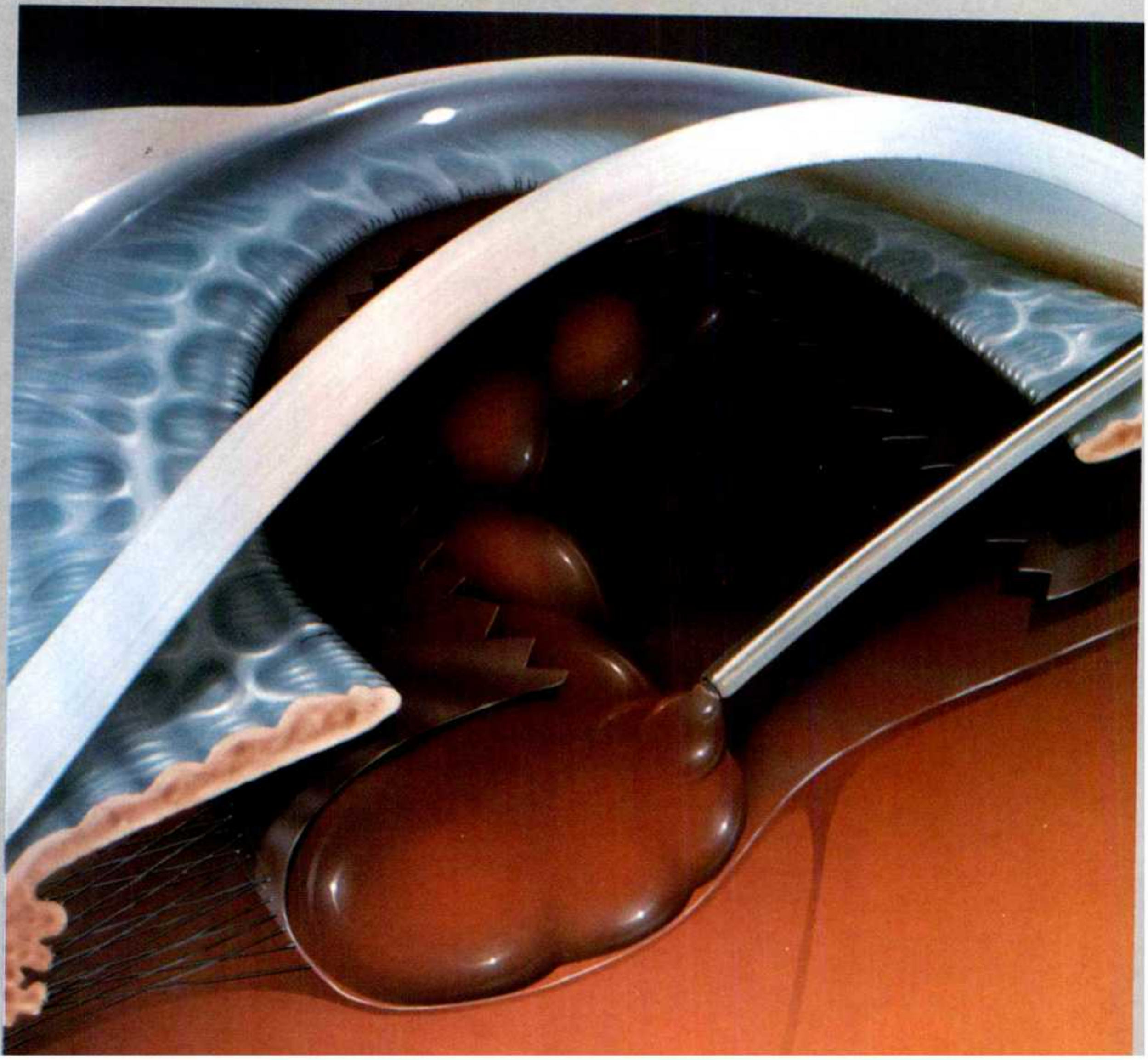

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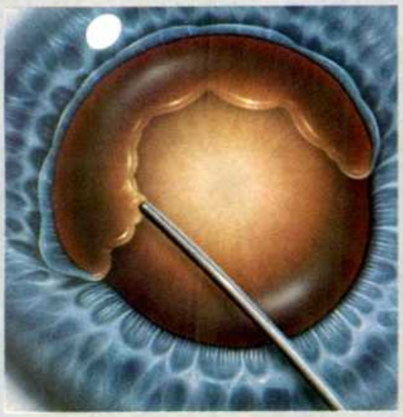

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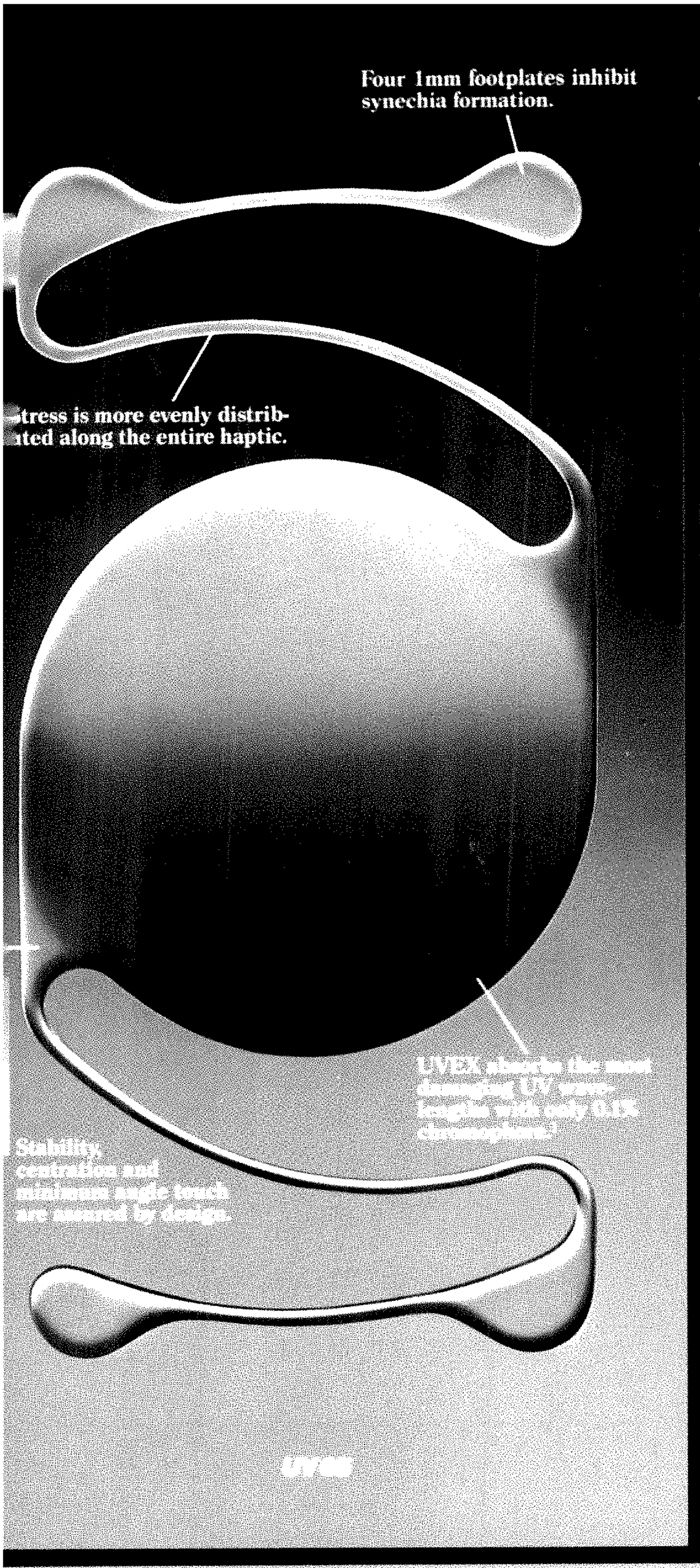
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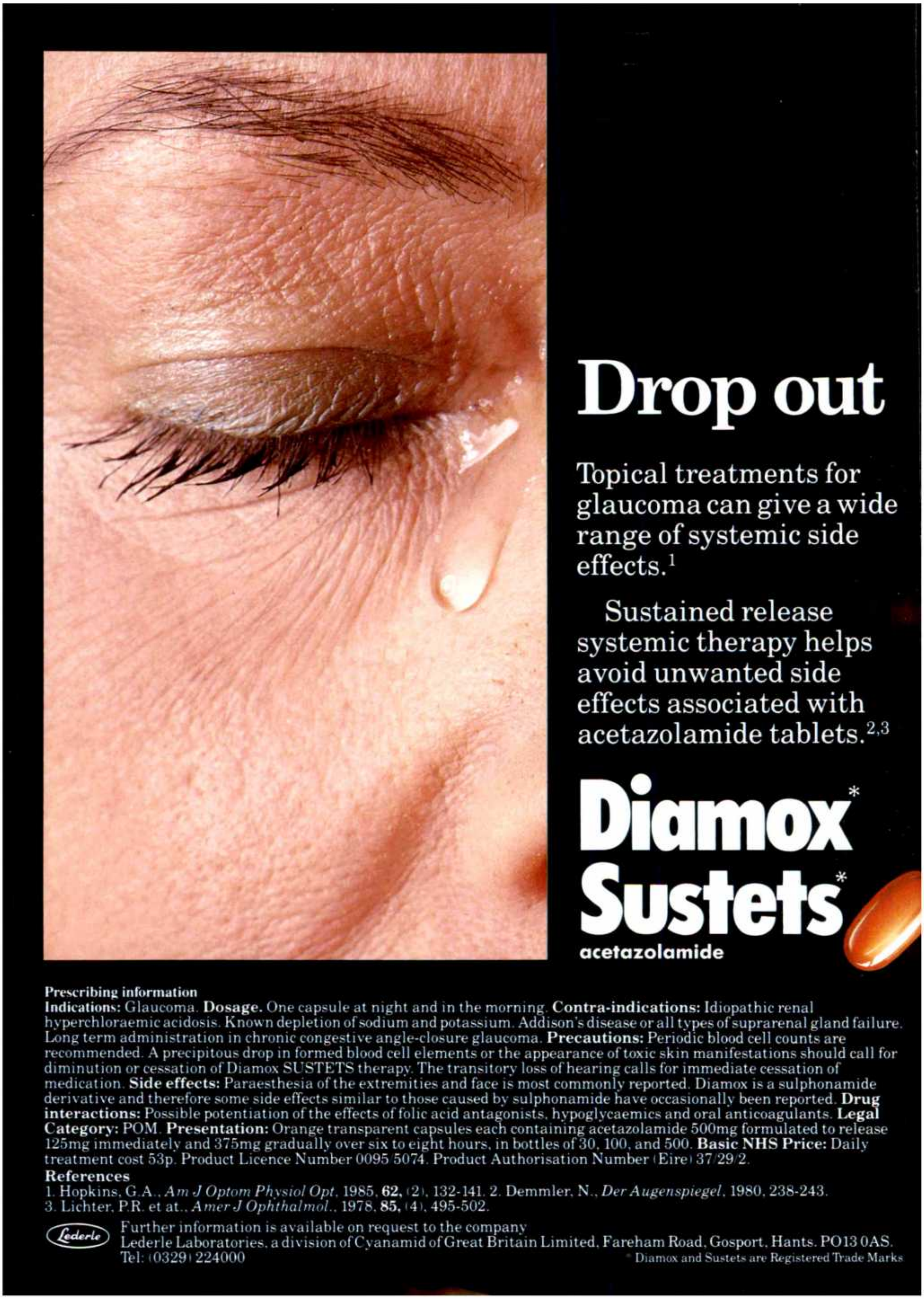

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British Journal of Ophthalmology, 1986, **70**, 877–878

Is acute glaucoma a symptom of diabetes?

MICHAEL CLARKE AND JONATHAN JAGGER

From the Western Ophthalmic Hospital, London NW1

SUMMARY Forty-three patients who had suffered an episode of angle closure glaucoma had an assessment of glucose tolerance. Two patients were known diabetics and one new diabetic was found as a result of the study. The prevalence of diabetes in this series did not differ significantly from the normal in view of the age distribution of the patients.

It has recently been reported for the first time that there is a high prevalence of diabetes in patients with closed angle glaucoma.[1] From a total of 142 patients 24 were found to be diabetic, only seven of these having previously diagnosed diabetes. A further 29 were found to have impaired glucose tolerance. This was a significantly increased number relative to a control group.

These results suggest that there are large numbers of patients with closed angle glaucoma who have undiagnosed diabetes. It is obviously important that this diagnosis should be made, particularly as long term treatment with miotics may prejudice the diagnosis and assessment of diabetic retinopathy.

We have studied a group of patients with closed angle glaucoma to determine whether any have undiagnosed diabetes.

Patients and methods

A total of 50 patients who had suffered from angle closure glaucoma were asked to return for assessment of their glucose tolerance. Forty-three patients attended. Two of them were known to have diabetes, and this diagnosis was accepted.

The remaining 41 patients had blood taken for blood sugar and glycosylated haemoglobin estimations following an overnight fast. If either of these results was abnormal, they were asked to return for an oral glucose tolerance test. The normal value for fasting blood sugar was taken to be ≤6·4 mmol/l[2] and that for glycosylated haemoglobin <8·0%.[3]

The oral glucose tolerance test was performed as laid down by the WHO committee guidelines.[4] That is, following an overnight fast blood was taken for fasting sugar estimation. A 75 g oral glucose load in 300 ml of water was then given to be drunk within five minutes. Venous blood sugar estimations were made at one and two hours after the glucose load.

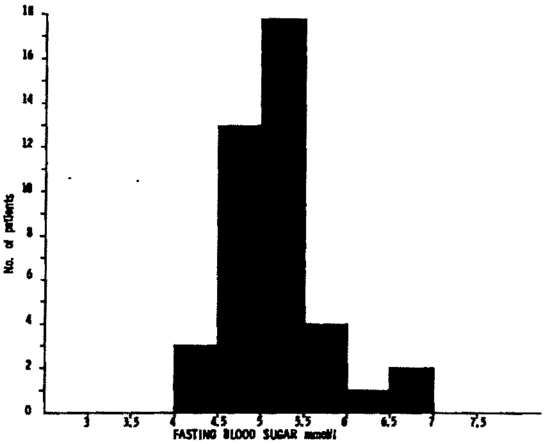

Fig. 1 *Distribution of fasting blood sugar concentrations.*

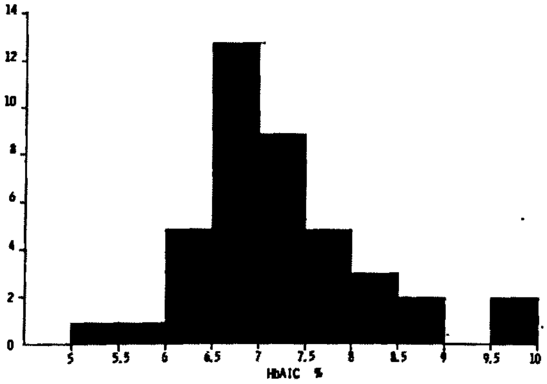

Fig. 2 *Distribution of HbA_1C values.*

Correspondence to D M Clarke, Bradford Royal Infirmary, Bradford BD9 6RJ.

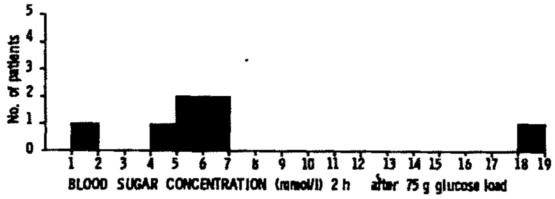

Fig. 3 *Distribution of blood sugar concentration two hours after 75 g oral glucose load.*

Diabetes was diagnosed if the fasting sugar was $\geqslant 8$ mmol/l or the two-hour sugar was $\geqslant 11$ mmol/l. Impaired glucose tolerance was diagnosed if the fasting sugar was <8 mmol/l and the two-hour specimen was >8 mmol/l but <11 mmol/l.

Results

The fasting blood sugar levels are shown in Fig. 1. Two patients had fasting blood sugars $>6\cdot4$ mmol/l and proceeded to oral glucose tolerance testing. Five other patients had $HbA1_c$ concentrations $>8\%$ (Fig. 2). These too were given oral glucose tolerance tests—a total of seven patients. The two-hour blood sugar concentrations after oral glucose load are shown in Fig. 3. It can be seen that only one patient had an oral glucose tolerance test diagnostic of diabetes and that no other patient had diabetes or impaired glucose tolerance. The results are significantly different from those of Mapstone and Clark[1] ($\chi^2=14$, $p<0\cdot001$), when patients with both diabetes and impaired glucose tolerance are compared but not when only those with frank diabetes are compared ($\chi^2=2\cdot60$).

Discussion

Only one patient in this series was found to have previously undiagnosed diabetes. Together with the two previously known diabetics this gives a prevalence of 6·99. This figure is compatible with the prevalence of diabetes among an unselected population of mixed Asian and European origin in West London,[5] the area from which the patients in this series were drawn, when the age distribution of the series is taken into account (Fig. 4).

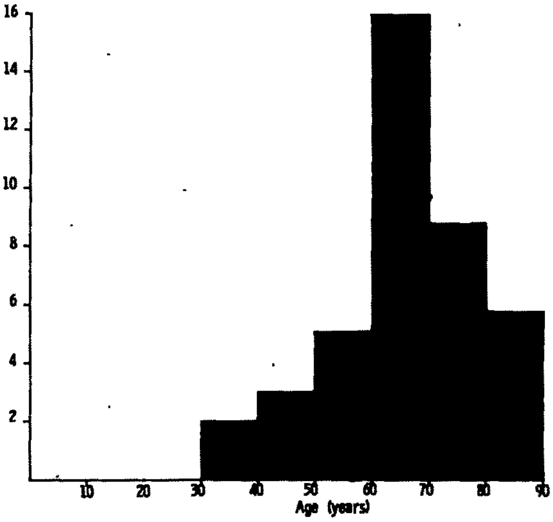

Fig. 4 *Age distribution excluding two known diabetics.*

On the basis of this study it seems unlikely that screening for diabetes among patients with closed angle glaucoma will uncover many undiagnosed diabetics.

The authors are grateful to Professor R F Fisher for statistical help and to the consultant staff at the Western Ophthalmic Hospital for permission to study their patients.

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Intraocular magnet of Parel

GERARD W CROCK, PATTABIRAMAN JANAKIRAMAN,
AND PRADEEP REDDY

From the Department of Ophthalmology, University of Melbourne

SUMMARY The intraocular magnet (IOM) is a new device based on permanent magnetism providing controlled energy for removal of magnetic intraocular foreign bodies. Its use is reported in 11 cases.

Retained intraocular foreign bodies remain an important cause of ocular damage despite the protective counselling of medical societies, industrial unions, insurers, and manufacturers.

The surgical management of general ocular trauma entered a new era with the development of vitrectomy,[1] while instrumentation for the removal of non-magnetic foreign bodies progressed pari passu.[2-4] By contrast the electromagnet, which is the mainstay in removal of magnetic intraocular foreign bodies, had been little changed since the days of Herschberg.[5] The disadvantages of these instruments are their bulk and clumsiness of handling, particularly if introduced within the globe[6] (Figs. 1 and 2).

This paper describes a new application of magnetism, as conceived by Parel, for intraocular use with or without vitrectomy techniques. Our first 11 cases of the successful removal of a foreign body by the intraocular magnet (IOM) are reported.

Material and methods

THE INTRAOCULAR MAGNET

The Parel magnet is composed of a rod 150 mm in length and 1·6 mm in diameter, set in a protective handle (Fig. 3). The magnetic rod is an aggregate of metallic elements, among which are rare earths. It is coated with gold, which is known to have little toxicity in the eye.[7]

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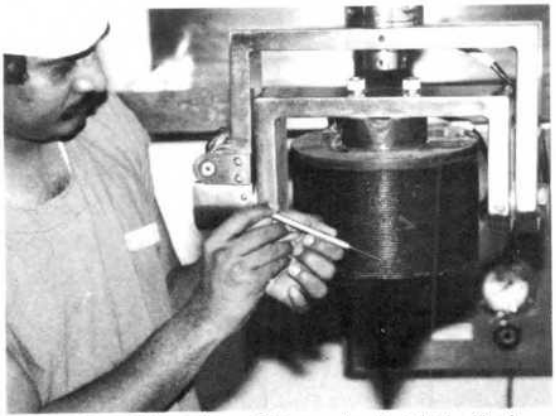

Fig. 1 *One of the authors (PR) standing beside the Haab giant electromagnet (1902) which is still to be found in the theatre suite at the Royal Victorian Eye and Ear Hospital, Melbourne. He is holding an IOM for comparison.*

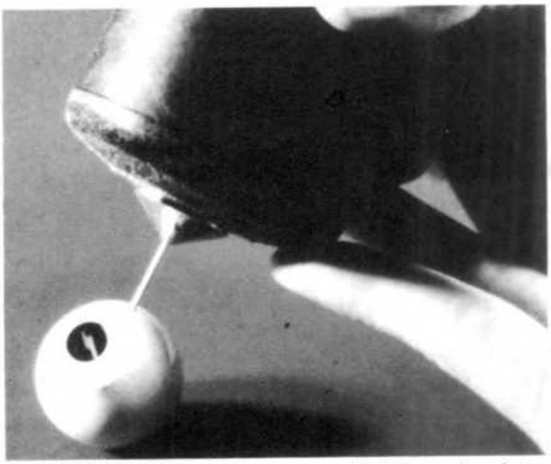

Fig. 2 *Hand-held Bronson magnet with Coleman's pole tip inserted through pars plana region of a model eye.*

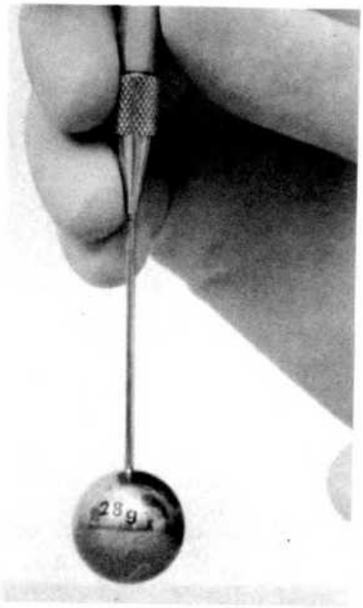

Fig. 3 *The Parel intraocular Magnet (IOM) lifting a 28 g steel ball.*

The surgical use of the older style electromagnets required a pole piece, usually cone shaped (Figs. 4A, B). Owing to the remoteness of its magnetic pole location (P) an electromagnet (EM) equipped either with a conical cone piece as in Fig. 4A, or with a cone extended and thinned to a 19 gauge intraocular probe (Fig. 4B), generates a feeble pull force at these tips relative to the magnetic force (F) of the main pole piece (P). Bronson went so far as to say that the pole tip has no application in foreign body surgery.[5]

The force-distance (F,e) graphs on the left of Figs. 4A and 4B, read in conjunction with schematic drawings, demonstrate how, in a quasi-uniform magnetic field, a non-encapsulated magnetic foreign body will accelerate rapidly. Angular misalignment (ß) of these instruments by the operator can cause unintentional incarceration of the foreign body within the globe (i), with subsequent complications.

The situation of the magnetic pull force with the IOM is illustrated in Fig. 4C. As the IOM magnetic pole (P) is located at the instrument tip itself, the risk of accident from misalignment becomes insignificant. The pull force (F) varies rapidly as the distance (e)

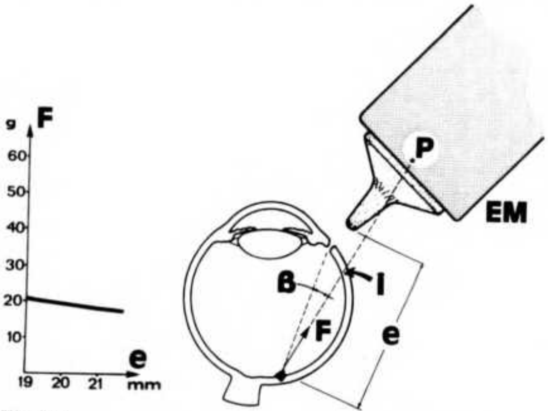

Fig. 4A

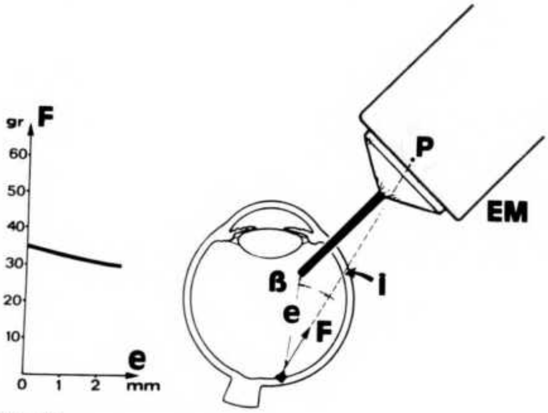

Fig. 4B

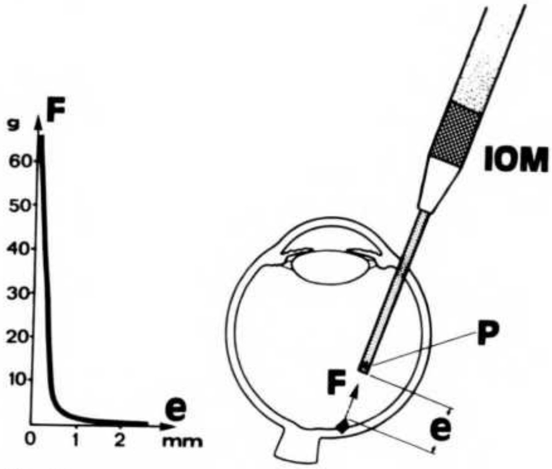

Fig. 4C

Fig. 4A, B, C *Schematic drawings to compare the physical differences in magnetic forces of the traditional electromagnet (EM) and the Parel magnet (IOM).* (A) *Standard conical pole piece fitted to an EM.* (B) *Coleman's pole piece fitted to an EM.* (C) *Rare-earth IOM.* (ß) *Misalignment angle resulting in secondary foreign body location at* (i) *(arrowed).* (e) *Distance between pole piece tip and foreign body.* (F) *Force vector applied to foreign body.* (g) *Grams.* (i) *Secondary location of foreign body.* (mm) *Millimetres.* (P) *Location of magnetic pole.*

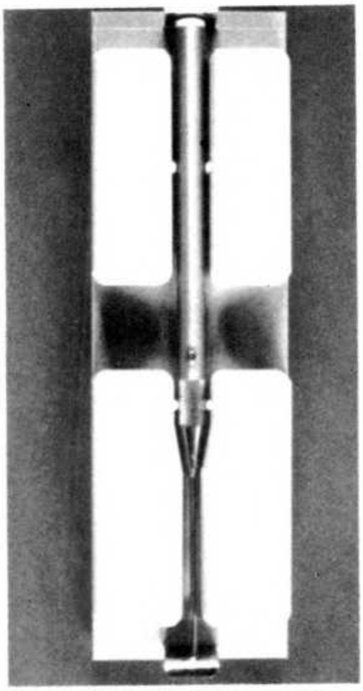

Fig. 5 *The IOM in its autoclavable storage container, which slows decay of the permanent magnet.*

from the magnetic object decreases. The graph on the left of the figure shows how a maximum force is obtained in contact with the foreign body. At a distance of 2 mm this force drops to zero, so that unwanted movements of intraocular magnetic foreign bodies are minimised with the IOM.

The IOM can be flash autoclaved in its storage container, which serves to slow down decay of the permanent magnet (Fig. 5). A bare IOM loses 10 to 15% of its pull force per year. When necessary, remagnetisation can be achieved readily by applying the rare earth IOM tip to the south pole of an electromagnet (EM) delivering at least 500 000 gauss. The IOM should be held to the EM central field axis with its tip touching the EM south pole piece. Remagnetisation takes less than one second.

Some of the giant EMs used in ophthalmology are capable of generating very strong magnetic fields. To utilise such ophthalmic EMs to recharge the IOM, care should be taken to: (1) Ascertain the accessible bare pole's polarity. Magnetic polarity reversal can be easily obtained by reversing the electrical current flow into the EM. The IOM will lose all its pull force if remagnetisation is attempted with an EM north pole piece. (2) Remove the usual conical pole piece and replace it with a flat one. The IOM should be held perpendicularly and at the centre of the flat pole piece.

OPERATIVE TECHNIQUE

The instrument has been designed free of the encumbrances of standard electromagnets, as an adjunct to vitreoretinal microsurgery. Adequate vitrectomy should be performed before the IOM is inserted into the posterior segment of the globe. The present model has a tip diameter of 1·6 mm. Its introduction into the eye, therefore, requires some enlargement of one of the standard sized entry ports commonly used with three-port pars plana vitrectomy techniques. The port should be enlarged after the preliminary vitrectomy has been completed. When intraocular foreign bodies have a greater diameter than the IOM, the port, as in case 5, may need extensive enlargement. Under ideal circumstances the manipulation of the IOM within the eye is done through the operating microscope. When location of the foreign body precludes this, or when media opacity compromises visibility through the operating microscope, recourse may be had to binocular indirect ophthalmoscopy.

Jackson Coleman described an iron pole piece which could be inserted inside an eye (Fig. 4B).[6] Previously when a pole tip was applied to the eye, even through the sclerotomy site, the magnet remained external. However, with Parel's instrument it is the magnet itself which enters the eye (Fig. 4C).

The fundamental difference in clinical behaviour of these two magnetic sources lies in the fact that the magnetic pole of the IOM is located at its very tip (Fig. 4C). The magnetic field of pull is therefore virtually coaxial with the instrument probe. By contrast a powerful electromagnet, having its pole outside the eye, can exert its magnetic pull over a wide field and may impact a foreign body into the wall of the eye ([i] arrowed in Figs. 4A and 4B) at some distance from its intraocular probe, which has only a very weak magnetic pull force.

Case reports

Case 1. A 37-year-old sheet metal worker presented on 31 May 1982 one week after his left eye was injured while working with a sledge hammer. Visual acuity was 6/6. There was a scleral entry wound at 10.30 o'clock near the limbus. The lens was clear. A foreign body track was visible through the vitreous. Above the optic disc was an area of choroidal and retinal haemorrhages. Below the disc was an encapsulated metallic foreign body (Fig. 6).

A three-port vitrectomy was performed two days after admission. The vitreous track and the capsule

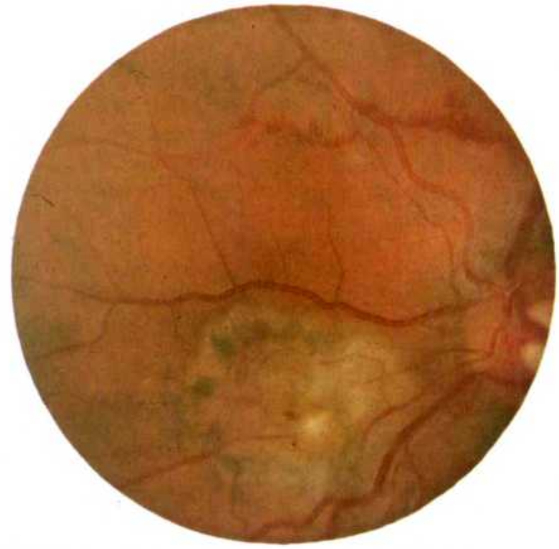

Fig. 6 *The dark mass of the encapsulated intraocular foreign body is highlighted by a white rim, and lies in a circular field of retinal pigment epithelial disturbance below the optic disc. A large, circular choroidal haemorrhage is seen above and nasal to the disc, skirted by retinal haemorrhage.*

overlying the foreign body were removed by the Intra Ocular Cutter (Micro-Fine Australia). The temporal port was enlarged to introduce the IOM. The foreign body was removed without incident. Postoperatively a vitreous haemorrhage developed centrally. This cleared spontaneously. When recorded on 14 June 1984, visual acuity was 6/18 and N 8, not improved with glasses, owing to posterior subcapsular lens opacity. This contrasted with a best acuity of 6/9 and N 4·5 in the early postoperative period.

Case 2. A 59-year-old male sheet metal worker sustained an injury to his left eye while grinding a gold-copper alloy. Fluctuating vision in this eye brought him to an ophthalmologist a year after the accident. Visual acuity was 6/6 uncorrected. There was a healed corneal scar superonasal to the visual axis and a localised traumatic cataract in the inferotemporal quadrant of the lens.

On fundus examination a foreign body could be seen in the superotemporal periphery attached to the retina by strands of vitreous, in which it lay just anterior to the retina. At operation on 25 June 1982 under binocular indirect ophthalmoscopic control the IOM was introduced through a superonasal sclerotomy 4 mm from the limbus and the tip approximated to the foreign body. Gentle manipulation freed the foreign body from the surrounding vitreous strands, and it was removed. Cryopexy was applied to the site of vitreoretinal traction in the area of the foreign body. The postoperative course was uneventful. Pinhole visual acuity one month postoperatively was 6/5.

Case 3. A 29-year-old metal press worker was struck by a flying metallic particle while operating a press. A corneal entry wound was present near the lower nasal limbus. The lens was clear. The intraocular foreign body was located on the retinal surface nasal to the disc in the immediate postequatorial region. Visual acuity was 6/4. On 4 August 1982 an attempt to extract the foreign body through a lower nasal sclerotomy with an electromagnet was unsuccessful. The case was then referred.

A three-port vitrectomy was performed two days later. It was not possible to view the foreign body through the operating contact lens and microscope. Therefore the IOM was approximated to the foreign body under indirect ophthalmoscopic control. During this procedure the retina adjacent to the foreign body was accidentally struck by the IOM, resulting in a subhyaloid haemorrhage which, though limited in volume, tracked immediately into the macular area. The foreign body was removed and cryopexy was applied to the site of impaction. Postoperatively the subhyaloid haemorrhage tracked into the remaining vitreous body. Five days later total vitrectomy, fluid/gas exchange, and encircling buckle was performed. Final visual acuity on 13 June 1984 was 1/60 and N 36.

Case 4. A 15-year-old male was shot in the right eye by an air gun pellet of 4·6 mm diameter. Visual acuity was perception of light. Examination under anaesthesia on 23 September 1982 revealed a ragged entry wound 12 mm in anteroposterior extent beneath the insertion of the medial rectus muscle and just above the long ciliary system. The corneal epithelium was hazy. There was a microscopic hyphaema. The lens was subluxated, and there was a massive vitreous haemorrhage inferiorly. Superiorly, extensive commotio retinae was observed. A gleam from the intraocular pellet could be seen in the 7 o'clock meridian near the vitreous base.

The medial rectus was reflected from its insertion. Prolapsed uveal and retinal tissue were reposited, and the large entry wound was closed with interrupted 8–0 nylon sutures. Then lensectomy and vitrectomy were performed through two horizontal ports. The temporal port was enlarged to introduce the IOM. The pellet was withdrawn to the pars plana after the temporal port had been further extended to deliver the foreign body through an incision, which was ultimately 6·5 mm in length circumferentially (Fig. 7). Partial fluid/gas exchange was performed after the foreign body was removed and cryopexy and buckling completed the surgery. The final visual

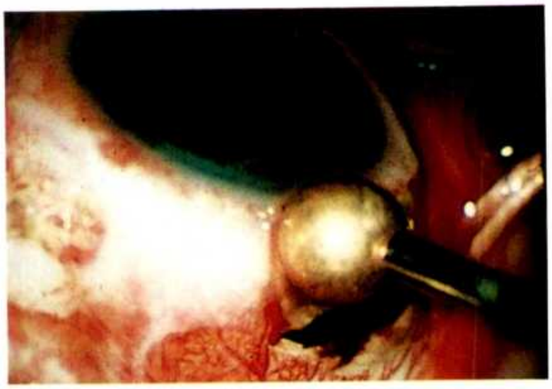

Fig. 7 *Magnetic air gun pellet (4·6 mm diameter) being delivered through a 6·5 mm port in the pars plana.*

acuity was hand movements. The retina was flat and the globe was hypotonic.

Case 5. A 22-year-old male carpenter was hammering a nail into timber. He was struck in the left eye by metallic foreign bodies, which lodged in the anterior chamber and in the vitreous base in the 6 o'clock meridian. There was a segmental traumatic cataract.

Both foreign bodies were removed by the IOM on 18 September 1982, one through the pars plana from a single port in the 2 o'clock meridian and the other through an inferior corneal section.

Two days later, because of progressive lens changes, lensectomy and vitrectomy were performed. Visual acuity on 14 June 1984 was 6/5 with a contact lens and N 5 with a +2·0 addition.

Case 6. A 27-year-old male sheet metal worker sustained a penetrating injury to his right eye when striking a stencil with a steel hammer. Visual acuity was 6/5. There was a corneal wound in the 3 o'clock meridian 2 mm inside the limbus. There was a hole in the underlying iris. The lens was clear. There was a patch of haemorrhage just nasal to the optic disc. *X*-ray localised the foreign body to be just in or behind the sclera. An attempt to remove the foreign body by electromagnet after disinsertion of the medial rectus was unsuccessful. The case was then referred on 7 December 1982.

. Ultrasongraphy showed the foreign body to be intrascleral. One week after injury laser burns were applied around the site of the foreign body (Fig. 8). Two days later, after posterior vitreous detachment was observed, a three-port vitrectomy was performed. The temporal port was enlarged to introduce the IOM. The foreign body was removed without incident after contacting the retinal surface under operating microscope control. An encircling buckle was applied. Visual acuity was 6/4 and N 4·5 with a −4·0 sphere on 2 June 1984. The postoperative fundus appearance is shown in Fig. 9.

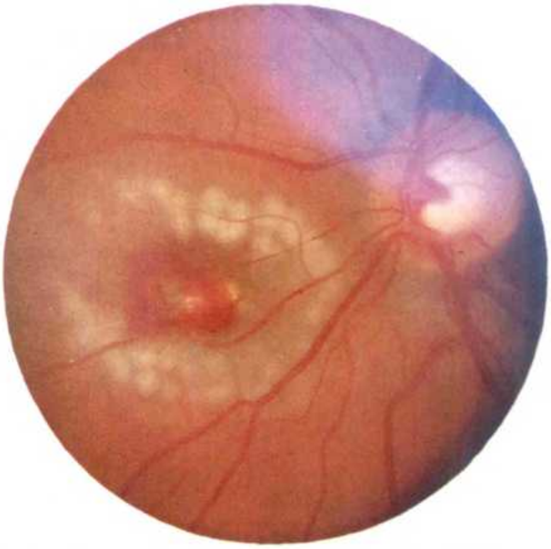

Fig. 8 *Fundus photograph showing recent laser burns around a metallic foreign body embedded in retina above and nasal to the optic disc, and capped with blood.*

Case 7. A 35-year-old male carpenter presented on 11 June 1983 with an intraocular foreign body below and nasal to the left optic disc following an injury while hammering a nail. Visual acuity was 6/12 with a pinhole. Attempted removal by hand magnet was unsuccessful. The case was then referred.

Four days later (15 June 1983) a three-port vitrectomy was performed, and the intraocular foreign body was removed through the upper temporal port with the IOM. Fluid/gas exchange, encircling buckle, and cryopexy of the foreign body impaction site completed the surgery. Visual acuity on 13 June 1984 was 6/6 with −3·0/−1·75 axis 90° and N 6 with a +1·5 sphere addition.

Case 8. On 1 October 1983 a 54-year-old male builder's labourer, dropped a length of steel rod and was struck in the left eye. Primary repair of a corneal laceration was carried out that day. The patient was referred on 5 October 1983 with a retained intraocular foreign body localised by radiography below the optic disc. A view of the fundus was precluded by lens opacity. A three-port lensectomy-vitrectomy was done on 6 October 1983 to reveal a small retinal tear below the disc and a larger one inferotemporally behind the equator. The intraocular foreign body was situated on the retinal surface adjacent to the large tear. The IOM was introduced through the upper nasal port and the foreign body removed. The retinal tears were frozen after fluid/gas exchange, and an encircling buckle was applied. Visual acuity recorded on 12 June 1984 had fallen from 6/6 in the early

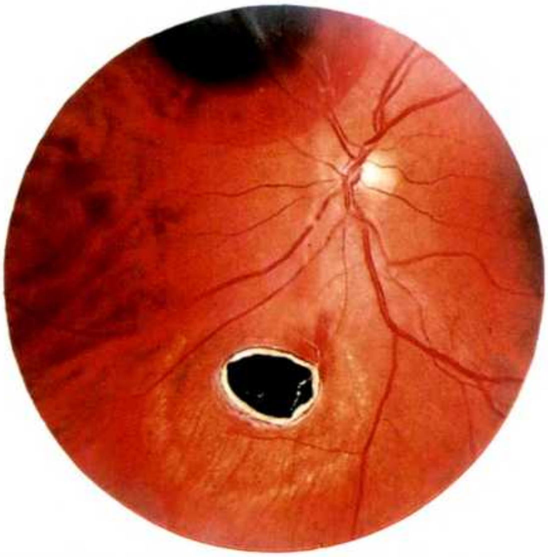

Fig. 9 *Postoperative fundus photograph showing foreign body site after removal by the IOM.*

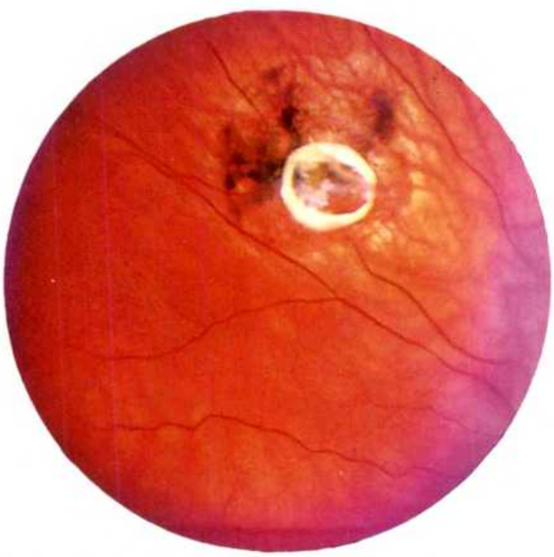

Fig. 10 *Foreign body capsule remnants following uncapping and removal by the IOM of an embedded metallic fragment.*

postoperative period to 6/60 due to cellophane maculopathy.

Case 9. On 22 October 1983 a 36-year-old housewife was hammering an iron bar. She presented on 25 October 1983 with a corneal wound, underlying lens opacity, and a foreign body which could be seen through the cloudy lens, encapsulated and lying on the retina inferonasal to the right optic disc. Visual acuity was hand movements. A three-port lensectomy-vitrectomy and foreign body removal by the IOM was performed on 28 October 1983. The capsule overlying the foreign body was nibbled away by the IOC before the IOM was inserted into the eye (Fig. 10). At review on 4 June 1984 vision was 6/9 with a contact lens and N 6 with a +3·0 addition.

Case 10. A 23-year-old male motor mechanic was striking a bearing with a chisel when he was hit in the right eye by a foreign body on 29 October 1983. Presenting visual acuity was 1/60. The fundus view was obscured by a shelving corneal wound and lens opacity. A foreign body was located in the mid vitreous cavity by *x*-ray.

On 30 October 1983 a three-port lensectomy-vitrectomy was performed, and the intraocular foreign body was removed via the upper temporal port. Fluid/gas exchange was performed without cryopexy or buckling. Vision corrected to 6/5 and N 4·5 with a contact lens in the immediate postoperative period.

He was readmitted on 17 May 1984 with an upper temporal balloon detachment and retinal dialysis. This was treated by external drainage, cryopexy, and encirclage. Seen on 15 June 1984, his vision had corrected to 6/9 with a +11·0 dioptre sphere and N 8 with a +3·0 addition.

Case 11. A 21-year-old male sheet metal worker was hammering a pin when he was struck in the left eye by a foreign body, which lodged in the mid vitreous. The anterior chamber was reformed with sodium hyaluronate, then the corneal laceration was repaired with 10–0 nylon. A three-port vitrectomy was made and the foreign body removed via the upper temporal port on 13 April 1984. Six days later lensectomy, fluid/gas exchange, and encirclage were performed. On 4 June 1984 pinhole vision was 6/24. There was irregular corneal astigmatism.

Discussion

The major application of the IOM lies in the removal of magnetic foreign bodies from the postequatorial segment of the phakic eye and from anywhere in the aphakic globe. It can be just as useful in the anterior segment, where it may be favourably combined with viscosurgery to minimise or avoid lens damage.

Eleven cases of retained magnetic intraocular foreign body have been reviewed with follow-up periods ranging from eight weeks to 23 months. All but one were in males.

Accurate localisation and adequate intraocular visibility are cardinal prerequisites to successful intervention with the IOM. If the foreign body is

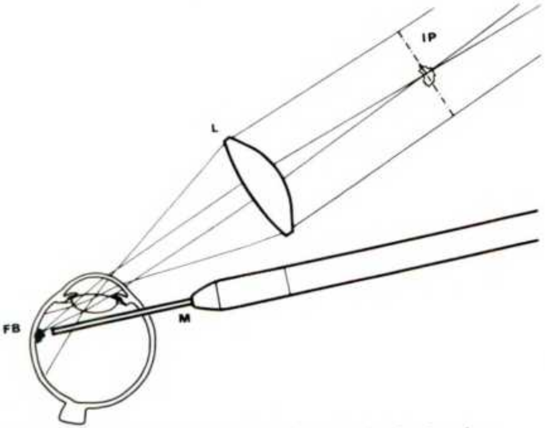

Fig. 11 *Shows indirect ophthalmoscopic viewing for control of the IOM. A small (34 mm) diameter condensing lens is essential. L=lens. FB=foreign body. M=magnet. IP=image plane.*

lodged outside the field of view of the operating microscope, or if haziness of the media precludes a clear view through the operating microscope, then the binocular indirect ophthalmoscope should be used. The latter method of visual control is hazardous and demands a high degree of skill. The operator must have a binocular view along the IOM so that the probe tip and the intraocular foreign body are virtually paraxial. To achieve this a small diameter (34 mm) condensing lens (Fig. 11) is mandatory.

In case 3 intraoperative concussion of the retina led to a limited preretinal haemorrhage, which tracked from its point of origin, superonasally, to the perimacular zone, with disastrous visual outcome (Fig. 12). Failure to appreciate the importance of the diameter of the condensing lens during paraxial viewing of the magnet rod against the fundus, through the binocular indirect ophthalmoscope, was responsible for this chain of events. The lens in question was of 20 dioptres with a diameter of 53 mm.

Size of intraocular foreign body has been correlated with final visual outcome.[8] Cases 4 and 8 bear out these statistics. The foreign body in case 4 was 4·6 mm in diameter. The massive impact resulted in phthisis bulbi. Case 8, with two retinal tears, one of which was quite large, had its final visual acuity compromised by premacular fibrosis.

Case 10 developed a retinal detachment due to dialysis within six months of removal of the intraocular foreign body. It must be assumed that the dialysis, which was found near the site of IOM introduction, had been induced by operative manipulation. We believe that limited vitrectomy and scleral buckling are desirable adjuncts to the successful removal of foreign bodies by the IOM.

The flying foreign body effect of electromagnets, applied at a distance from an intraocular foreign body, often resulted in further disruption of intraocular structures during surgical removal and accounted in no small part for some of the disheartening statistics reported.[8] Parel's application of permanent magnetism represents a significant step towards the controlled use of magnetic force in closed eye microsurgery. Further miniaturisation of intraocular magnets has already been achieved (Parel J M, personal communication).

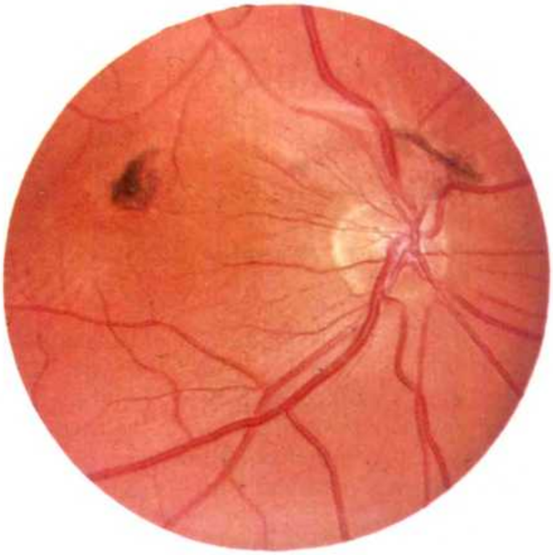

Fig. 12 *Postoperative fundus photograph from case 3. The pigmented macular scar was caused by a haemorrhage which migrated from a point of retinal concussion inadvertently made with the IOM. Operator error was occasioned by use of a 53 mm diameter indirect ophthalmoscopic condensing lens.*

The authors are grateful to Drs J Heinze, J Yeung, and J Reich for cases 1, 2, and 5.

Jean-Marie Parel, Director of the Ophthalmic Biophysics Center of the Bascom Palmer Eye Institute, University of Miami, invented the IOM. We are extremely grateful to him for the opportunity to have been among the first to use this instrument.

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Pathogenesis of pupillary capture after posterior chamber intraocular lens implantation

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SUMMARY Pupillary capture is an unusual complication of posterior chamber intraocular lens implantation and may occur in the early or late postoperative period. We describe a series of patients with early or late onset pupillary capture and describe the pathogenesis. Early capture results from mechanical factors and is usually preventable. Late capture may be mechanical but is usually a sequel to the formation and subsequent contraction of iridocapsular synechiae. Synechiae result from lens epithelial or iris stromal hyperplasia and myofibroblastic metaplasia; they may be minimised by an atraumatic technique and adequate control of postoperative inflammation. The effect of pupillary capture is largely cosmetic, and we encountered no specific complications attributable to it.

Posterior chamber intraocular lenses (IOLs) are the most common type of IOL inserted at cataract extraction in the USA.[1] An uncommon complication is pupillary capture or entrapment. Pupillary capture (PC) occurs when part of the pupil margin is displaced posteriorly behind the IOL optic, which then appears to lie in the anterior chamber.[2]

PC is more frequently described as an early event, although a late form is recognised.[2-6] Early PC is attributed to mechanical factors, while late PC is not adequately explained. A variety of pharmacological and surgical corrective manoeuvres have been described.[2 4 6-8]

We have seen a number of patients with either early or late PC. All patients had normal pseudophakic anatomy at the completion of surgery, but developed PC at intervals ranging from one day to two months postoperatively. In this paper we report our findings and relate them to the pathophysiology of the eye after extracapsular cataract extraction and posterior chamber IOL implantation.

Materials and methods

We performed a prospective study of pupil and IOL relationships in patients undergoing routine extracapsular cataract extraction (ECCE) and IOL implantation. All IOLs had anteriorly angled haptics. All patients had been noted to have normal pseudophakic anatomy at the conclusion of surgery. In the postoperative period any uveitis was controlled with intensive topical dexamethasone before discharge. Patients were included in the study if PC was diagnosed in the immediate postoperative period or at follow-up. PC was classified as early if diagnosed in the first five days after surgery and as late if diagnosed later.

Results

Fifteen patients with PC of a posterior chamber IOL were identified. The time of onset ranged from 1 to 60 days postoperatively, mean 30 days. The patients ranged in age from 51 to 85 years, mean 69 years. Eight patients were female. These patients were seen during a period when 480 ECCE and IOL implantations were performed, yielding an incidence of PC of 3·1%. All cases of PC have been seen in patients with ciliary sulcus fixated posterior chamber IOLs. To date no patient with an 'in the bag' posterior chamber IOL has developed PC.

Two patients suffered early PC; in one of them it was reversed but late PC subsequently developed. The second patient with early PC did not respond to initial intensive pharmacological attempts at reversal, but the condition spontaneously reversed three months later, with no evidence of residual posterior synechiae formation.

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Fourteen patients suffered late PC. At diagnosis of late PC large numbers of pigmented deposits on the IOL were frequently observed, and many patients had a persistent iritis. No complications attributable to the PC were seen.

Patients with late PC had many factors associated with ocular inflammation and iris trauma (Table 1), and only one patient had an unremarkable course. Thirteen of these patients had late PC resulting from the formation of iridocapsular synechiae with displacement of the pupil margin. These iridocapsular synechiae were found to be continuous with and adherent to zones of posterior capsular opacity. One patient suffered late reversible mechanical PC.

Pre-existing ocular diseases included glaucoma in two patients and single patients with prior excision of iris melanoma and broad iridectomy, diabetic maculopathy, senile macular degeneration, and amblyopia.

ILLUSTRATIVE CASES

Case 1. A 74-year-old Indian male on treatment for chronic open angle glaucoma underwent routine ECCE and posterior chamber IOL implantation by a junior staff member. On the first postoperative day PC was diagnosed and treated successfully with initial pharmacological mydriasis and later miosis. At discharge four days later the pupil was free, with no evidence of PC. The pupil margin remained free at initial follow-up visits. The patient developed a marked postoperative uveitis with questionable compliance, and by two months postoperatively had developed synechial pupil capture.

Case 2. A 60-year-old West Indian female had previously undergone trabeculectomy for glaucoma and had residual posterior synechiae. A broad iridectomy with ECCE and IOL implantation were performed, with normal pupil-IOL relationships in the early postoperative period and at first follow-up visit. The patient did not comply with treatment and presented four weeks after surgery with a marked iritis and posterior iridocapsular synechiae formation behind the IOL, forming PC.

Table 1 *Predisposing factors in 14 patients with late pupil capture*

Preoperative:	Prior iritis	4
	Posterior synechiae*	4
	Prior surgery†	2
Operative:	Difficult surgery‡	6
	Broad iridectomy§	4
	Peripheral iridectomy	3
Postoperative:	Severe postoperative iritis	6
	Poor compliance	5
	Wound leakage	2
	Acute PC	1
	Uneventful course	1

*Three due to prior iritis, one to prior trabeculectomy.

†One trabeculectomy; one iris melanoma excised three years previously.

‡Includes cases with intraoperative iris trauma, and those where technical difficulties in expressing the nucleus, aspirating cortex, maintaining the anterior chamber, or inserting IOL were encountered.

§Three intraoperative; one three years previously for iris melanoma.

Case 3. A 60-year-old Caucasian was seen two weeks after routine ECCE and IOL implantation for a Nd-YAG laser capsulotomy. The IOL position was normal, and the pupil was then dilated. Spontaneous pupil capture developed, but was subsequently reversed with topical thymoxamine. No further episodes of PC were observed.

Discussion

Early onset PC is the result of mechanical factors such as wound leakage with shallow anterior chamber, pupillary dilatation, air in the anterior chamber forcing the iris behind the IOL, or reversal of IOL, and is more frequently seen in IOLs with planar haptics than other types.[2-7] Mechanical factors appear to be responsible for all cases of early PC, but may cause recurrent or even late PC (case 3). This form of PC results from movement of the free pupil margin behind the IOL optic owing to the relative anterior displacement of the IOL, or the relative posterior displacement of the pupil margin. Subsequent synechiae formation may preclude non-surgical reversal. Of our two cases of early mechanical PC one was reversed by mydriatics while the other was not. In the latter patient the condition subsequently reversed spontaneously. Reversal manoeuvres that have been described include mydriasis with external limbal haptic massage and subsequent miosis,[2 4] Nd-YAG laser-induced mechanical shock-wave lens retropulsion,[8] and direct surgical manipulation.[5] Other authors advocate no intervention.[3 4 6] Our patients suffered no apparent ill effects of early PC.

Late PC is seen two weeks to nine months postoperatively (Pearce J, personal communication). Although it may occasionally be mechanical in origin (case 3), it is more frequently synechial in origin. Our observations indicate this latter type to be the result of iridocapsular synechiae formation about the edge of the IOL optic, with subsequent contraction pulling the iris posteriorly (Fig. 1). Several changes in the early postoperative period contribute to synechiae formation between the iris margin and the posterior capsule. Immediately after ECCE fibrinous strands extend from the anterior capsule edges towards the posterior capsule, with which they subsequently make contact.[9] Remnants of the anterior capsular lens epithelium proliferate in response to factors

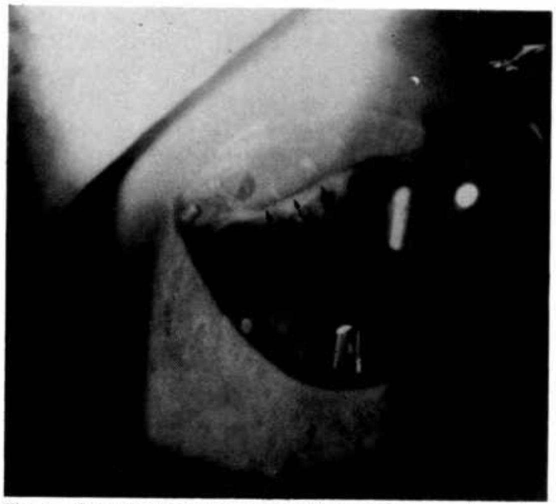

Fig. 1 *Synechial pupil capture with posterior capsular striae and opacification. Arrows delineate iridocapsular synechiae behind IOL.*

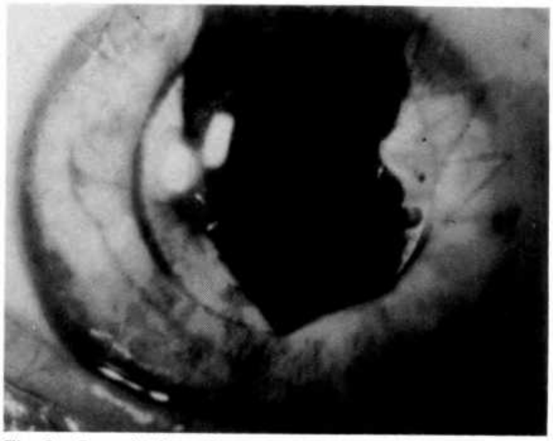

Fig. 3 *Synechial pupil capture following ECCE, broad iridectomy, and inferior sphincterotomy in a patient with prior iritis and extensive posterior synechiae. Iridocapsular synechiae (arrows) are continuous with posterior capsular opacity.*

present in the aqueous of injured eyes.[10] These proliferating lens cells extend on to the posterior capsule, where they spread and undergo myofibroblastic metaplasia.[11,12] This process, resulting in a variety of fibrous posterior capsular opacities, is more extensive and severe in younger patients, who have larger numbers of active lens cells, and may opacify the visual axis.[11,12] In older patients, with fewer viable lens cells and less lens epithelial metabolic activity, the process is largely limited to the area of anterior to posterior capsule contact.[11] The importance of viable lens epithelium in the process of fibrous metaplasia is illustrated by Fig. 2, the case of an elderly male who had undergone ECCE for a morgagnian cataract. In such a cataract the lens epithelial cells are necrotic, and fibrous metaplasia from this source cannot occur. In neither the early nor late postoperative period did this patient develop synechiae, and both his anterior capsule remnants and posterior capsule remained entirely free and clear at 12 months after ECCE and even six months after secondary posterior chamber IOL implantation.

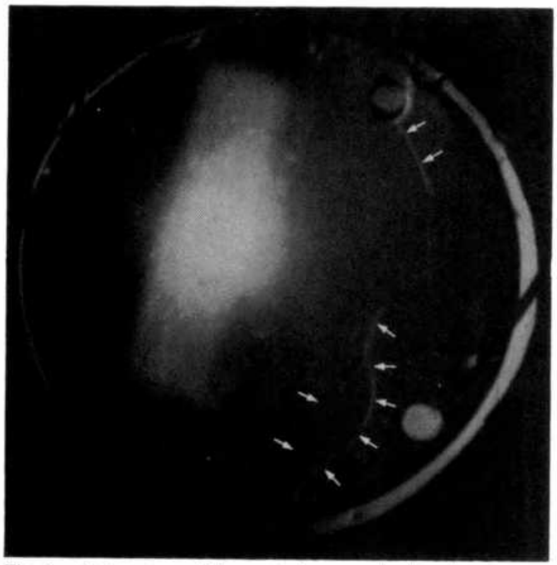

Fig. 2 *Appearance of free anterior capsular flaps between IOL and posterior capsule six months after secondary IOL implantation. Note clear edges of anterior capsule remnants, with absence of fibrosis or opacification.*

Fibrous metaplasia in the anterior segment does not originate only from lens cells, but may also occur from inflamed or traumatised iris tissue.[13,14] Iritis of any origin is frequently accompanied by the formation of synechial adhesions. In experimental ECCE uveal cells are observed to form bridges from the anterior uveal epithelium to the anterior and posterior capsule.[13] Our clinical observations support these experimental findings. In our patients iris and pupil margin trauma were a prominent feature (Fig. 3). This indicates that the presence of iris trauma, with iris cell release, contributes to the process of synechiae formation between the pupil margin and the posterior capsule round the IOL optic. It is noteworthy that uveal cells have been found to form a significant component of the posterior capsular opacification seen after experimental ECCE.[13] Cells of iris origin, in association with lens epithelial cells, play an important part in the formation of both iridocapsular synechiae and of posterior capsular opacification. Reduction of iris manipulation and trauma during ECCE may be important in preventing both pupil and posterior capsule complications. While some surgeons advocate resuturing broad iridectomies, it is not likely that this would reduce the total number of uveal cells released into the anterior chamber, but may mechanically keep the iris plane more anterior.

The question arises whether the IOL itself may directly trigger some of the processes involved in PC. Macrophages are deposited on the surfaces of most IOLs soon after implantation as part of a foreign body reaction.[15-17] These cells can subsequently undergo metaplasia to fibroblast-like cells[16] and may contribute to synechiae formation about the IOL edges, particularly in the presence of iris trauma or inflammation. While macrophages may contribute, it appears that posterior iridocapsular synechiae arise largely from iris and lens epithelial myofibroblastic metaplasia.

We found late PC to be most commonly a synechial event resulting from iridocapsular synechiae, with subsequent contraction drawing the pupil margin posteriorly. In a histopathological study of eyes at necropsy, posterior iridocapsular or iridovitreal synechiae were observed in 14% of eyes with posterior chamber IOLs.[18] In our patients severe iritis or iris trauma were noteworthy risk factors. At the time of diagnosis of PC the IOLs frequently had large numbers of pigmented deposits which have been shown to be macrophages.[17] In several patients these deposits have made posterior capsulotomy with the Nd-YAG laser more difficult. In addition, because these patients have a fixed pupil, fundus examination and treatment is compromised. We have not observed any other complications of synechial PC.

In conclusion, acute PC is usually due to mechanical factors which may be avoided by scrupulous attention to surgical detail. Late PC may occasionally be a reversible mechanical phenomenon, but is more commonly a sequel to iridocapsular synechiae formation and contraction. Synechial PC is more often seen after difficult surgery, iris trauma, severe iritis, or poor patient compliance.

We thank Mr Ron Marsh and Mr Redmond Smith for access to patients under their care and for helpful comments, and Ms Sue Ford for photographic assistance.

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Visual evoked potential latency and contrast sensitivity in patients with posterior chamber intraocular lens implants

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SUMMARY An electrophysiological investigation of visual evoked potential (VEP) latency and contrast sensitivity was performed in a group of 13 patients who had undergone extracapsular cataract surgery with posterior chamber lens implantation. In spite of good postoperative visual acuity, abnormalities were detected in nine of the group (69%). This study suggests that, even with successfully implanted lenses, there may be a reduction in visual function which could be the result of altered transmission through the plastic lenticulus or fibrosis of the posterior lens capsule, and/or subtle changes in retinal architecture, not observed ophthalmoscopically.

The optical disadvantages of spectacle lenses in the correction of aphakia make intraocular lenses (IOLs) an attractive alternative. Although intraoperative and postoperative complications have been widely reported, improvements in both lens design and surgical technique have reduced these problems, so that lens implantation is increasingly widely practised. In the USA alone it has been estimated that the implantation rate exceeds 500 000 annually,[1] and that posterior chamber lenses account for nearly two-thirds of these, the remainder largely comprising anterior chamber implants. There is also an increasing trend towards using IOLs in the UK, a recent survey suggesting that 45% of cataract operations involved the use of lens implants.[2]

The success of an implanted lens can be judged on the basis of low complication rate and by assessment of eventual visual acuity. On the basis of an acuity of 6/12 or better a success rate of over 90% has been reported with posterior chamber implants[3-5] and 87% in patients who have undergone intracapsular lens extraction with insertion of an anterior chamber implant.[6] Visual acuity may, however, be normal in the presence of a variety of disorders in which overall contrast sensitivity is reduced.[7] This is the type of visual impairment in which some patients report 'fogginess' or 'haziness' of vision despite achieving normal standards of visual acuity. In a recent report Hess *et al.*[8] have detected abnormalities in contrast sensitivity, measured psychophysically, in patients with iris clip lenses inserted after intracapsular cataract extraction. As an alternative to psychophysical means, contrast sensitivity function can be estimated electrophysiologically by recording visual evoked potentials (VEPs).[9] These are known to be influenced not only by retinal and optic nerve pathology but also by factors affecting the quality of the visual image on the retina, such as opacities of the media, refraction, and pupil size (for review, see Halliday[10]). On theoretical grounds alone it would appear that abnormalities in the VEP are likely to be seen in patients with IOLs.

We believe there have been no reports so far on electrophysiological changes in patients who have undergone intraocular lens implantation. We report here the results of a bimodal approach which has determined VEP latency and contrast sensitivity in 13 patients with good visual acuity following extracapsular surgery and posterior chamber IOL insertion.

Patients and methods

PATIENTS

Thirteen patients (age 57–70 years, mean 65·4 years) who had undergone successful extracapsular

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Correspondence to Mr J W Howe.

cataract extraction with insertion of a posterior chamber IOL were examined (Table 1). Each had a corrected visual acuity of 6/12 or better in the pesudophakic eye, with no clinical evidence of retinal or optic nerve pathology and a normal intraocular pressure (21 mmHg or less). In 10 of these patients there was a variable degree of cataract in the contralateral eye, but in the remaining three the cataract had been unilateral and the visual acuity in the fellow eye 6/6 or better. Results from these patients were compared with a normal, age matched population from our database (mean age 62·6, SD 9·3, n=55).

ELECTROPHYSIOLOGY

A checkerboard stimulus was produced by a video pattern generator on a high quality TV monitor. In the first part of the test luminance modulation of the pattern was selected to give the pattern reversal mode of stimulation. The checksize of the stimulus was 50′ and the visual field subtended, 17°×14°. The overall luminance of the TV screen—both with and without pattern—was maintained constant at 10 Cd m^{-2}. Pattern contrast (defined as $(L_{max}-L_{min})/(L_{max}+L_{min})$ where L_{max} and L_{min} were the luminance of the bright and dark checks respectively) was adjusted to be 95% with a reversal rate of 2 per second.

The second part of the test, to measure contrast sensitivity, was performed with the onset-offset mode of stimulation. The rationale for the selection of this type of pattern modulation is fully discussed elsewhere.[9] The pattern was present for 40 ms every 500 ms (note: the presentation rate—as with pattern reversal mode—was locked to the 50 Hz monitor frame rate). Using a check size of 19′ for patients with

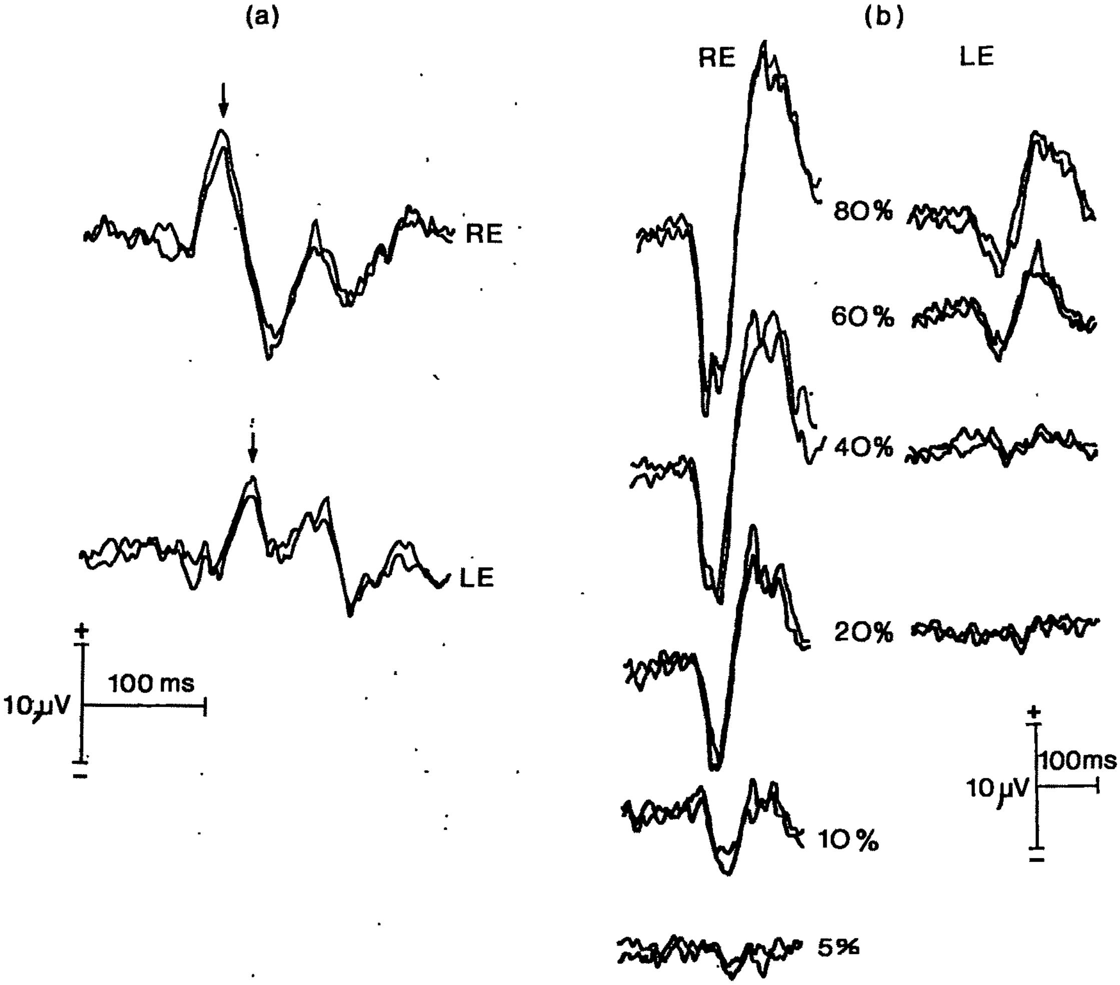

Fig. 1 *VEPs from patient No. 7 (LE pseudophakic RE normal). Pattern reversal responses are shown in column* (a) *and onset-offset responses at different contrast levels in column* (b).

a VA of 6/9 or better and 25′ for those with an acuity of 6/12, we made recordings at (usually) five contrast levels between 5% and 80%. These were selected in a pseudorandom sequence to try to eliminate any possible order effects. The patients were given short periods of rest between each contrast measurement so as to minimise fatigue and any concomitant increase in response variability.

Silver/silver chloride disc electrodes were attached to the scalp with collodion, in the following positions: active—Oz; reference—Cz; earth—Pz.

A Medelec electrophysiological recording unit was used to amplify, average, and store the evoked potentials. The amplifier bandwidth was 0·8–80 Hz, and either 64 or 128 epochs of 300 ms duration were averaged depending on the size of the response. Two averages were obtained at each contrast level to check for consistency, and quantitative analysis was performed on the average of these two. A peak-peak amplitude measure was adopted: in the case of the pattern reversal VEPs it was that between P100 and N150, in those to onset-offset it was between components CI and CII. A permanent record of the responses was made on an X-Y plotter. Amplitude data from the traces were then fed into a MINC PDP-11 computer for storage and further analysis. Monocular stimulation was adopted in all investigations, the subject being instructed to maintain fixation and focus on a small LED marker attached to the centre of the screen. This was checked during the investigation by closed circuit TV monitoring. Before the start of the test the subject was preadapted to the luminance of the blank screen for 5 minutes. This was the only source of illumination in an otherwise darkened room. The test was concluded with the measurement of the subject's pupils under experimental conditions.

Results

In Fig. 1 the responses from a patient with a left intraocular implant and visual acuities of 6/6 in each eye are illustrated. The pattern reversal responses indicated a delay in the main P100 component in the pseudophakic eye as compared with the RE. The onset-offset responses clearly showed reduced amplitude at all contrast levels in the LE. When the amplitude of these responses was plotted against log contrast (Fig. 2), significant differences between the two eyes were observed, not only in amplitude but also in the electrophysiologically estimated contrast threshold (arrowed).

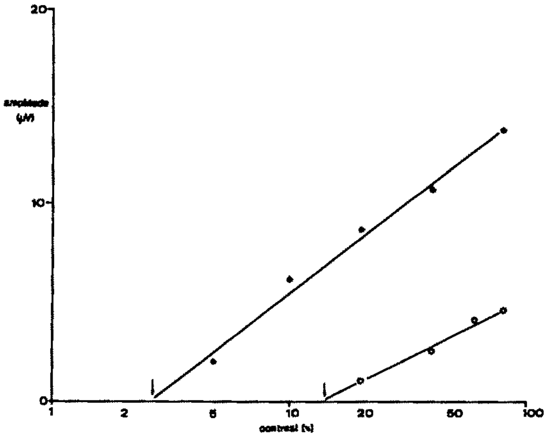

Fig. 2 *Amplitudes of the onset-offset responses from patient No. 7. (Fig. 1) plotted against log-contrast. Closed symbols (●)=normal RE. Open symbols (○)=pseudophakic LE.*

In Table 1 data concerning all 13 patients in the study are presented. P100 latency was significantly increased (at the 1% confidence level) in four of the group, and increased contrast threshold in eight. It is of interest that three of the four patients showing abnormal latency also had abnormal contrast thresholds. In addition, and perhaps of greater interest, is the fact that four patients with normal latencies showed elevated thresholds. In the group as a whole nine of the 13 patients showed some electrophysiological abnormality.

Table 2 shows the data concerning the three patients in whom it was possible to perform interocular comparisons, as the contralateral eye was normal. Interocular difference in latency was significant in two of the three patients (though the third was only marginally outside the 1% confidence level), and all three showed greater latencies in the pseudophakic eye. Interocular threshold differences were

Table 1 *Visual acuity, VEP latency, and contrast threshold in pseudophakic eyes*

Serial no.	*Age*	*VA*	*P100 Latency (ms)*	*Contrast threshold (%)*
1	60 (M)	6/6	134·0*	3·3
2	61 (M)	6/9	115·0	5·0
3	69 (M)	6/6	122·0	15·0*
4	64 (F)	6/6	125·0	3·9
5	57 (F)	6/9	114·0	7·7*
6	70 (M)	6/12	102·0	10·9*
7	65 (F)	6/6	138.0*	13·8*
8	66 (F)	6/6	113·0	8·6*
9	70 (F)	6/9	111·0	4·6
10	61 (M)	6/9	132·0*	5·2*
11	68 (M)	6/6	110·0	3·9
12	69 (M)	6/12	129·0*	11·9*
13	70 (M)	6/6	105·0	6·1*

*Significant at 1% level.
Normal P100 latency=113·0 (SD 6·2) ms (99% CL=128·0 ms) (n=55). Normal contrast threshold=2·1 (SD 1·3)% (99% CL=5·1%) (n=49).

Table 2 *Interocular comparison in those patients with pseudophakia and a normal contralateral eye*

Serial no.	*VA*		*Diagnosis*		*P100 Latency (ms)*			*Contrast Threshold (%)*		
	RE	*LE*	*RE*	*LE*	*RE*	*LE*	*(ΔI)*	*RE*	*LE*	*(Δt)*
3	6/9	6/6	Normal	Pseudophakia	116·0	122·0	(6·0)	3·2	15·1	(11·9)*
7	6/6	6/6	Normal	Pseudophakia	112·0	138·0	(26·0)*	2·8	13·8	(11·0)*
10	6/9	6/5	Pseudophakia	Normal	132·0	125·0	(7·0)*	5·2	2·4	(2·8)*

*Significant at 1% level.
Normal interocular latency difference ΔI = 2·0 (SD 1·9)ms (99% CL = 6·3 ms) (n = 55).
Normal interocular threshold difference Δt = 0·8 (SD 0·8)% (99% CL = 2·7%) (n = 49).

significant in all three patients, and again higher values were observed in the operated eye.

Discussion

Before it is possible to attach pathological significance to a delayed and/or attenuated VEP or depressed contrast sensitivity (that is, increased threshold) several confounding causes must be eliminated. To this end special attention was given to the selection of patients with good central acuity and no evidence of any retinal or optic nerve disorder as judged by careful ophthalmoscopy, perimetry, and fluorescein angiography. In all patients the corneae were clear on slit-lamp examination, and no significant vitreous opacities were observed. The posterior capsule was intact in all patients. The size of the pupil can also be a source of error, as miosis reduces retinal illumination, which in turn increases VEP latency. Pupillary diameter was directly measured and was not significantly different from the normal range; it was never less than 3 mm in any of the eyes investigated, thus being excluded as a possible causal factor. At the average luminance of the stimulator the eyes were adapted to a low photopic level. The pupils were therefore partially dilated under these conditions, and this would theoretically increase the amount of distorted light due to spherical aberration, which can be an important consideration in IOL design.[11] This blurring could produce a reduction in contrast, though we were unable to detect any correlation between pupil size and contrast sensitivity.

Visual acuity was measured on a conventional Snellen chart, viewed under photopic conditions (approximately 10 times the average luminance of the TV stimulus), and therefore the patient's pupils would be more constricted, reducing the influence of peripheral distortion. From this reasoning we would speculate that, if the contrast sensitivity experiment was performed under photopic conditions (for example, 100 Cd m^{-2}), the observed differences in contrast sensitivity in pseudophakia may be attenuated or even disappear, and conversely, performed at reduced luminance (for example, 1 Cd m^{-2}), the difference may be enhanced.

The delayed pattern reversal VEPs in 31% of the patients and reduced contrast sensitivity in 61% were probably due to poorer light transmission through the optic media, in particular the intact posterior capsule or the implant itself. Although the posterior capsule fibrosis did not appear to be clinically significant, it could still explain some of our findings by virtue of its position on or near the nodal point of the eye, since pathological evidence frequently shows fibrosis and membrane formation.[12] However, our data do not preclude the possibility that some of these changes may have resulted from subtle alterations in retinal architecture resulting from mild postoperative cystoid macular oedema, which was not ophthalmoscopically apparent.

The reason for the difference in detection rate in the two VEP measures was most likely due to differences in the stimulus. The pattern reversal stimulus was very coarse, utilising very large checks at high contrast. Experiment has confirmed that this form of pattern modulation, in conjunction with checks of subtense >20′, elicits VEPs which tend to respond to the luminance of the individual checks as well as the spatial contrast between them. This luminance modulation effect would tend to overcome to some degree any reduction in spatial contrast of the retinal image produced by opacification within the media. The onset-offset mode of stimulation, however, produces VEPs which have much purer components to spatial contrast, and when contrast sensitivity was investigated by this approach the detection rate of these latent contrast changes was much enhanced. The checksize used in this part of the experiment (19′ or 25′) determined contrast sensitivity in the 'mid-range' of the total contrast sensitivity function (which is approximately equal to the maxima found in the function when it is obtained psychophysically to sinusoidal grating, that is, at 2 cycles $degree^{-1}$). The data therefore do not allow us to make predictions on whether overall contrast sensitivity was diminished, though the fact that all patients had a good standard of visual acuity suggests that sensitivity to small, high contrast elements near the resolution limit was unaffected.

In conclusion, our data show that it cannot be assumed that a good standard of central acuity measured postoperatively in pseudophakic patients, necessarily implies 'normal vision'. We would submit that the role of contrast sensitivity testing as a means of assessing the efficacy of an IOL implant, either by psychophysical methods or by using evoked potentials as we have done, has merit as a useful adjunct in the clinical management of these patients.

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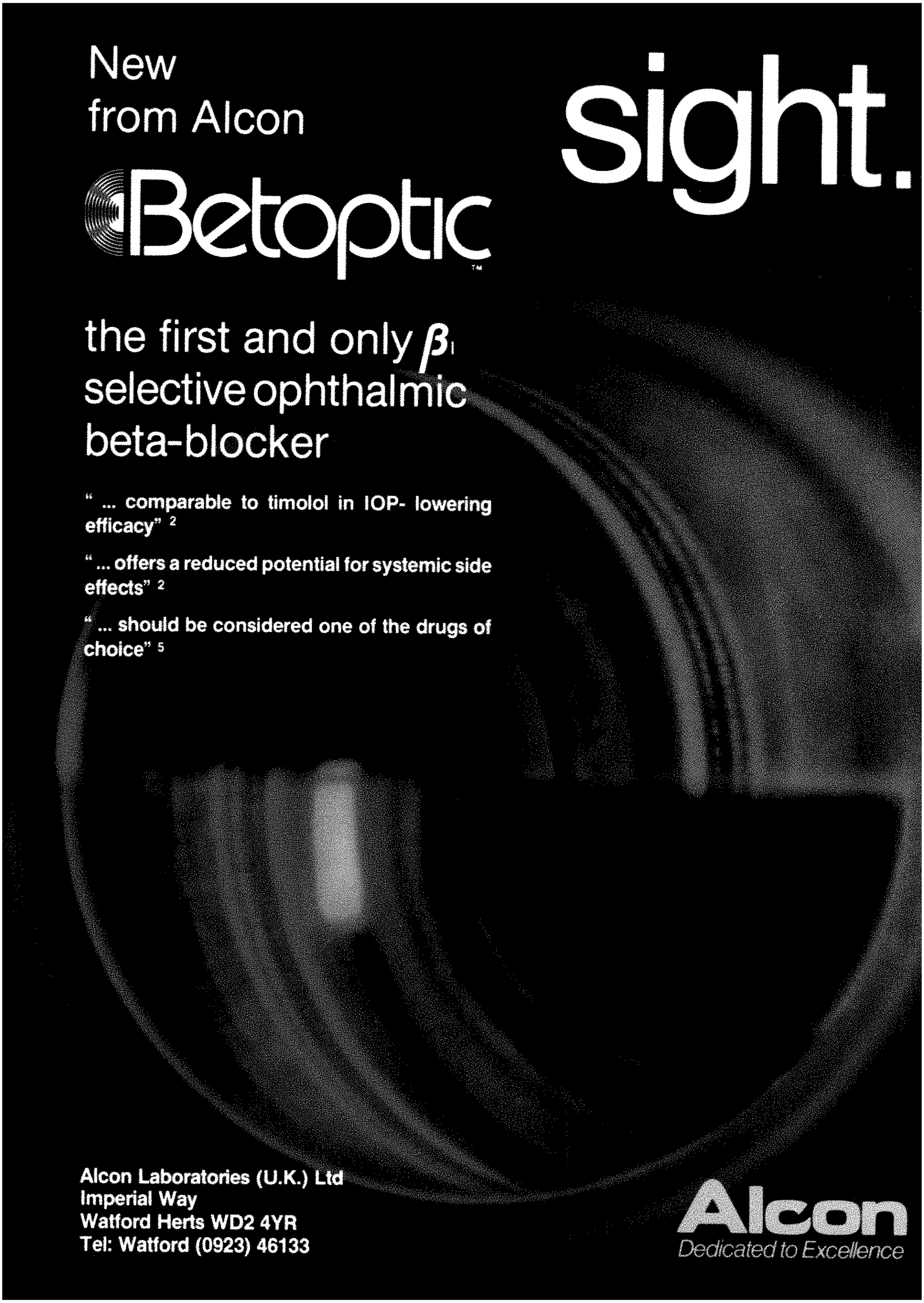

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EFERENCES: 1. Berrospi A. R. and Leibowitz H.M. Betaxolol. A new beta-adrenergic blocking agent for treatment of glaucoma. Arch. Ophthalmol. **100** 943-946 June 1982. **2.** Berry D.P., et al., Betaxolol and Timolol. A comparison efficacy and side effects. Arch. Ophthalmol. **102** 42-45 January 1984. **3.** Levy N.S., et al., A controlled comparison of Betaxolol and Timolol with long-term evaluation of safety and efficacy. Glaucoma **7** 54-62 March-April 1985. Schoene R.B., et al., Effects of topical Betaxolol, Timolol and placebo on pulmonary function in asthmatic bronchitis. Am. J. Ophthalmol. **97** 86-92 January 1984. **5.** Stewart R.H., et al., Betaxolol vs Timolol. A Six-Month uble-blind comparison. Arch. Ophthalmol. **104** 46-48 January 1986. **6.** Van Buskirk, E.M., et al, Betaxolol in patients with glaucoma and asthma. Am J Ophthalmol. **101** 531-534 May 1986. **7.** Data on file at Alcon Research and velopment.

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Ultrastructural pathology of melanomalytic glaucoma

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SUMMARY A patient presented with a heavily pigmented ciliary body tumour accompanied by diffuse pigmentation of the iris and chamber angle and secondary open angle glaucoma. The case was diagnosed clinically as malignant melanoma and melanomalytic glaucoma, and the eye was enucleated. Routine histopathology, immunohistochemistry, and ultrastructural studies revealed the tumour as being of the spindle cell type with extensive necrosis accompanied by a massive macrophagic response. The iridocorneal angle was heavily infiltrated by large pigmented cells, which were identified as being predominantly melanomacrophages. This is consistent with the few previous descriptions of this condition and confirms the view that the aqueous outflow obstruction is simply a mechanical process. Most of the native trabecular endothelial cells, which had also phagocytosed large quantities of melanin, still maintained their normal relationship to the trabeculae, though there were signs of activation. Immunohistochemistry and electron microscopy revealed the presence of moderate numbers of tumour cells on the iris surface and in the trabecular meshwork distant from the primary tumour site. The importance of these findings to the management of anterior uveal melanomas with secondary open angle glaucoma is discussed.

Secondary open angle glaucoma in cases of malignant melanoma of the anterior uveal tract is due to cellular obstruction of the outflow pathways.[1] Tumour cells which have been shed from the neoplasm may be carried in the aqueous and become trapped within the trabecular meshwork, or the cells may directly proliferate within the chamber angle and meshwork as in ring melanomas. A different pathogenetic mechanism appears to underlie 'melanomalytic glaucoma',[2 3] a rare condition in which spontaneous necrosis of an iris or ciliary body melanoma is accompanied by a massive macrophagic response and raised intraocular pressure. Large melanin laden macrophages block the uveal surface and intertrabecular spaces of the outflow system. The term 'melanomalytic glaucoma' was coined by Yanoff and Scheie[2] because they considered the disease mechanism to be similar to phacolytic and haemolytic glaucoma, in which obstruction of outflow pathways is due to macrophages laden with lens material and haemorrhagic debris respectively.[4 5]

In the only previous electron microscopic investigation of the outflow system in a case of melanomalytic glaucoma[3] the majority of the cells causing obstruction were believed to be exogenous macrophages. In addition Van Buskirk and Leure-du Pree[3] observed melanophagocytosis by native trabecular endothelial cells which were also becoming detached from the trabeculae, and they postulated that these cells may have played a role in blocking the aqueous outflow pathways. Tumour cells were not found in the angle or trabecular meshwork in this case.

We here describe a case which was considered on clinical and histopathological grounds to be melanomalytic glaucoma. However, immunohistochemistry and transmission electron microscopy revealed the presence of tumour cells within a predominantly melanomacrophagic infiltration. The aim of the study was to establish morphological criteria for the indentification of melanomacrophages, trabecular endothelial cells, and tumour cells within the outflow pathways.

Materials and methods

CLINICAL DETAILS

In June 1982 a 60-year-old Caucasian male presented to his general practitioner with blurred vision in the left eye. He was subsequently seen by an ophthalmologist and was found to have heterochromia iridis, a pigmented mass in the peripheral iris and ciliary body in the superonasal quadrant, and an intraocular

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pressure (IOP) of over 50 mmHg. The patient was referred to Glasgow (September 1982), where investigation led to the diagnosis of ciliary body melanoma and melanomalytic glaucoma. The tumour encroached locally on to the posterior corneal surface, the iris, and the trabecular meshwork between the 9–11 o'clock positions, but the iris and trabecular meshwork throughout 360° were lined by a carpet-like sheet of pigmented tissue. The lens, vitreous, retina, and choroid appeared normal. The optic disc showed 0·6 cupping. The IOP remained high (>50 mmHg) despite thorough antiglaucoma therapy.

The possibility of conservative management was considered, and a trabeculectomy and iridotomy were performed to reduce the IOP and also to determine the nature of the infiltration of the angle distant from the main tumour mass.

Positive identification of viable tumour cells on a sponge used to collect the aqueous and in the trabecular meshwork led to the decision to enucleate the eye one week later. The globe was fixed in 2% cacodylate buffered glutaraldehyde.

The patient is alive and well at the present time.

PATHOLOGICAL EXAMINATION AND IMMUNOHISTOCHEMISTRY

An oblique pupil-optic nerve block and small segments from the superior and inferior calottes were taken for routine paraffin histopathology (Fig. 1), with conventional staining and bleaching techniques.

The heavy pigmentation of the cells in the anterior segment rendered immunohistochemical studies by the peroxidase-antiperoxidase (PAP) procedure unsatisfactory. Accordingly serial sections were mounted on gelatin and chromalum coated slides and were treated with acidified potassium permanganate (0·25%) and bleached in 2% oxalic acid. The reagents employed were α_1 antitrypsin (α_1 AT), α_1 antichymotrypsin (α_1 ACT) (Dakopatts, Denmark) and anti-S100 antibody (Dakopatts, Denmark). The antigen-antibody complex was successfully visualised with amino ethyl carbazole, with haematoxylin as a counterstain. DAB, B galactosidase, and 4 chloro-1-naphthol gave unsatisfactory results.

The calottes were cut in meridional slices as shown in Fig. 1.

PREPARATION FOR MICROSCOPY

Representative blocks of limbal tissue were processed in the conventional fashion and embedded in Araldite. Semithin sections (1–2 μm) were stained with toluidine blue. Ultrathin sections (50–90 nm) were stained with uranyl acetate and lead citrate and examined in a Philips 301 transmission electron microscope. The blocks of limbal tissue, cornea, and iris (Fig. 1a) taken for scanning electron microscopy (SEM) were critical point dried, mounted on aluminium stubs, coated with gold, and examined in a JEOL JSM T200.

Results

ROUTINE HISTOPATHOLOGY

The tumour, which measured 6×5×5 mm (Fig. 1b)

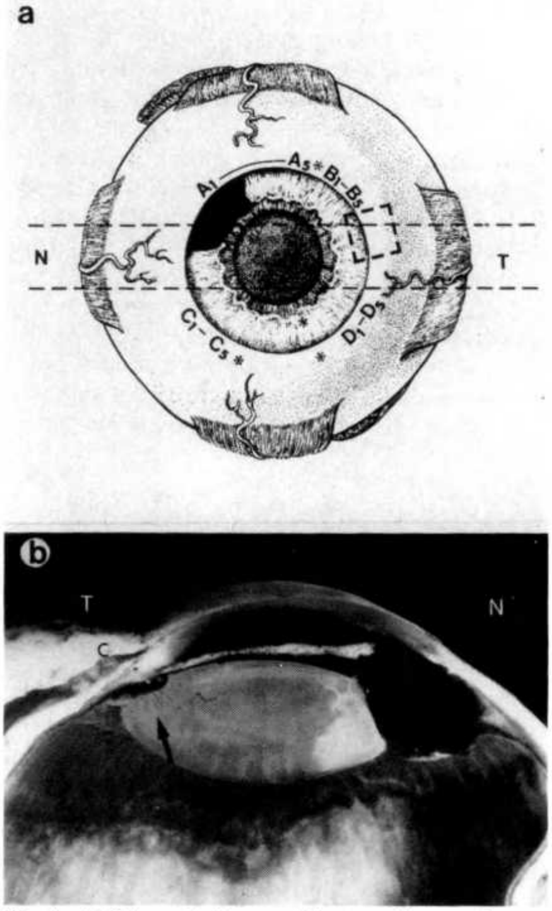

Fig. 1 (a) *Schematic diagram of the eye to illustrate the position of the tumour in the superonasal quadrant. The cuts made to remove the pupil-optic nerve block for routine histopathology are indicated by the horizontal broken lines. The trabeculectomy site is represented by the broken box. Tissue blocks for SEM were taken from the areas adjacent to the asterisks. The position of the individual meridional slices of limbal tissue taken from the superior and inferior calottes for ultrastructural studies are indicated* (A1–5, B1–5, C1–5, D1–5). (b) *Macroscopic view of the globe after removal of the superior calotte showing the ciliary body melanoma and adjacent lens opacity, the conjunctival bleb* (C) *over the site of the trabeculectomy, and fine pigment dusting of the zonular fibres (arrow).* N=*nasal,* T=*temporal.*

was a malignant melanoma of spindle cell type. It showed extensive areas of necrosis (Fig. 2) filled with debris and melanomacrophages. Identifiable tumour cells were found only on the posterior corneal surface, in the iris root, and in the pars plana (Fig. 2a). A mixture of macrophages and viable tumour cells (Fig. 2b) extended on to the iris surface and around the chamber angles; on the temporal aspect they had infiltrated the scleral drainage flap, the suprachoroidal space, and conjunctival flap. The trabecular meshwork in paraffin blocks from the superior and inferior calottes contained heavily pigmented cells, which could not be accurately identified even in bleached sections.

The lens showed a secondary cataract (Figs. 1a, 2a), and the retina and optic nerve showed changes typical of secondary glaucoma.

IMMUNOHISTOCHEMISTRY

The reagents (α_1 AT, α_1 ACT) for the identification of macrophages showed the profusion of these cells in the chamber angle and within the trabecular meshwork (Fig. 2c). Cells staining positively with anti-S100 antibody could be identified scattered within the inner meshwork and within the infiltrate on the anterior iris surface (Fig. 2d).

ULTRASTRUCTURAL PATHOLOGY

Tumour morphology

In both blocks taken from the edge of the tumour (A_1 and A_2 in Fig. 1) islands of viable spindle B melanoma cells were found along the posterior corneal surface (Fig. 3a). The tumour cells had a low melanin content, which contrasted with the heavily pigmented macrophages, and showed the characteristic features of spindle melanoma cells, namely a large ovoid nucleus, which was sometimes indented, with a variable chromatin pattern and coarse nucleolonema, a large nuclear-cytoplasmic ratio, premelanosomes of types I–III, lipid inclusions, and

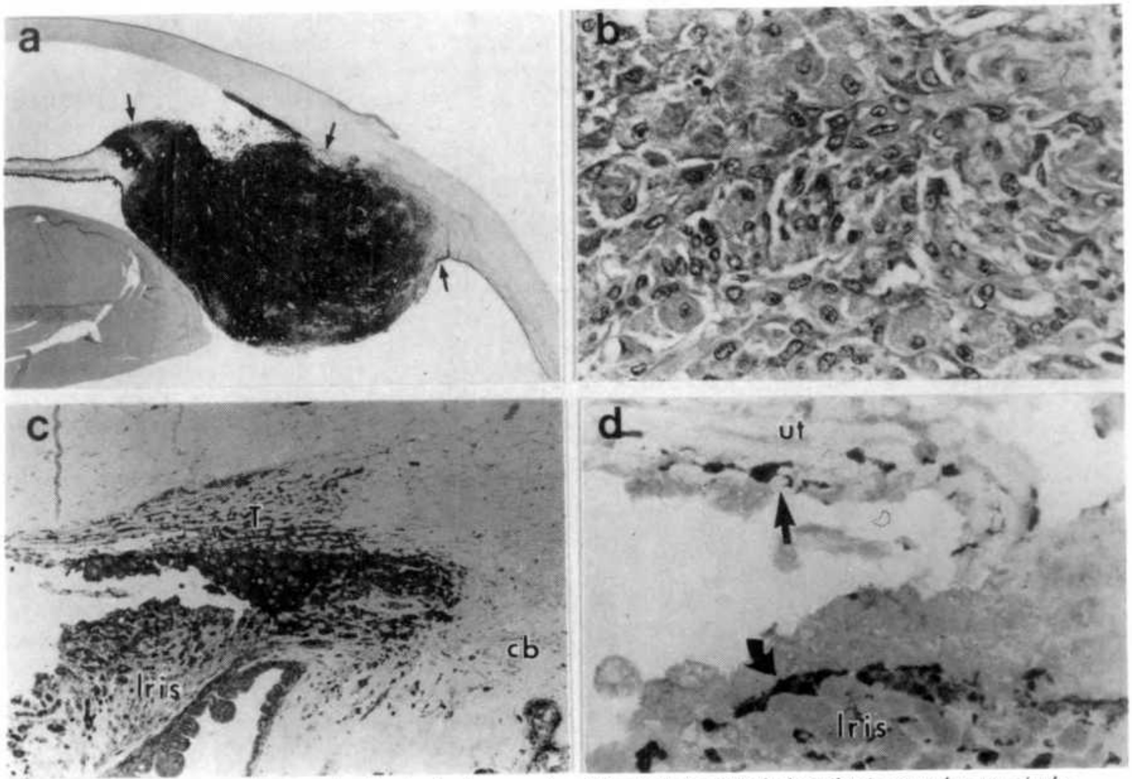

Fig. 2 (a) *Light micrograph of routine histological preparation (H and E) showing the heavily pigmented tumour in the ciliary body and iris. Islands of identifiable tumour cells were noted at the positions indicated (arrows).* (b) *Bleached preparation of the tumour showing spindle melanoma cells among larger rounded cells.* (c) *Immunohistochemical demonstrations of large numbers of α_1 antichymotrypsin-positive cells (macrophages), and* (d) *S100 positive cells (tumour cells) in bleached paraffin sections of the chamber angle from the inferior calotte. Note the occasional S100 positive cell in the uveal meshwork (straight arrow) and on the iris (curved arrow) beneath the rounded macrophages.* T=*trabecular meshwork,* cb=*ciliary body,* ut=*uveal trabeculae. Magnifications:* (a) ×*12·5,* (b) ×*260,* (c) ×*63,* (d) ×*260.*

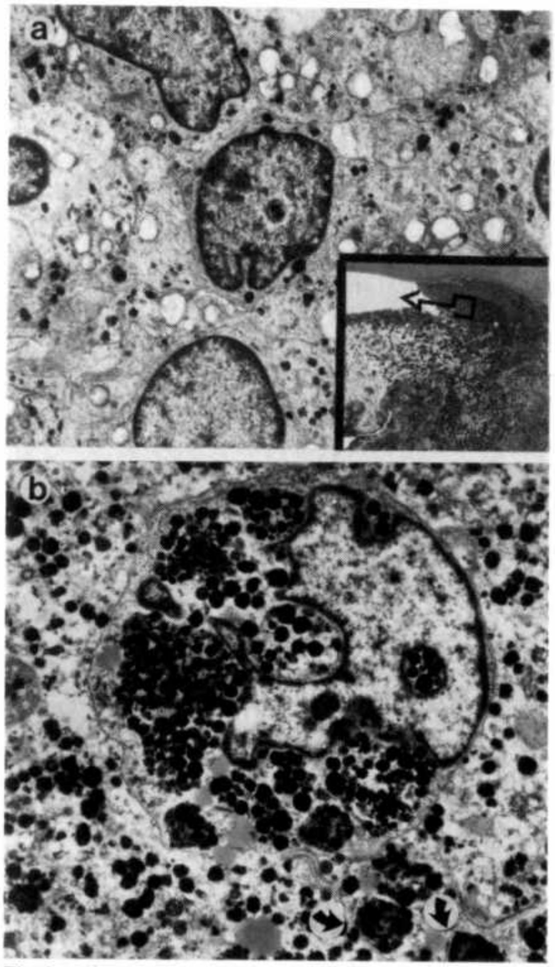

Fig. 3 *Electron micrographs of* (a) *an area of viable melanoma cells (block* A_2*) and (b) a zone of necrosis (block* A_1*). The cells shown in* (a) *were from an island of 'amelanotic' cells which had proliferated along the posterior corneal surface (see inset—semithin section). Note the numerous, complex, interdigitating cell processes of these tightly arranged spindle melanoma cells, in transverse section; nuclear indentation and sparse granular premelanosomes.* (b) *Large quantities of free cell debris, especially melanin, in the extracellular space within necrotic areas of the tumour. Some of the melanin is contained within compound lysosomal complexes (arrows) similar to those present in the large melanin laden macrophage, which shows evidence of cell necrosis. Magnifications:* (a) *×4774, inset ×29,* (b) *×4340.*

abundant free ribosomes (Fig. 3a). Within the necrotic areas of the tumour there were large quantities of free melanin granules, lipid-like inclusions, lysed cell organelles, and membranes (Fig. 3b). Large rounded melanomacrophages were identified within but more especially around the necrotic zones (Fig. 3b), and there was evidence of death of macrophages in situ. This was manifest as rupture of plasma membranes and nuclear fragmentation, but in addition large compound melanophagolysosomes identical to those found within the cytoplasm of macrophages were distributed in the extracellular space among the rest of the cell debris (Fig. 3b).

In other areas of the tumour viable melanoma cells were interspersed among large numbers of giant melanomacrophages (Fig. 4a). There was a wide variation in the morphology of the melanoma cells. The melanin granules occurred either as oval individual premelanosomes in various stages of maturity, or as uniformly electron-dense, round, mature melanin granules (Figs. 4b–d). Even in those cells containing mature melanosomes there was a great deal of variation in their density within the cell cytoplasm (Figs. 4a, d). The melanin within the macrophages was characteristically within large (0·3–7·0 μm) membrane bound lysosomal complexes (Fig. 4a). These melanophagolysosomes contained numerous melanosomes in various stages of melanogenesis, but occasionally there were also individual melanosomes within some macrophages.

The anterior surface of the iris in all the specimens studied was carpeted by large, globular, pigment laden macrophages several layers thick resting on a layer of tumour cells (Fig. 5).

Chamber angle and aqueous outflow pathways

The iridocorneal angle recess in all the blocks investigated by light microscopy and scanning and transmission electron microscopy contained large numbers of giant globular melanomacrophages. This was particularly evident in the blocks from the inferior angle (Figs. 6, 7). In the majority of the blocks studied these cells obstructed the intertrabecular spaces on the inner surface of the uveal meshwork (Figs. 6, 7a). The anterior ciliary muscle face and iris root as well as all the available inter- and intratrabecular spaces in the trabecular meshwork were also penetrated by heavily pigmented macrophages (Figs. 6a, b), which often assumed very large proportions (up to 50 μm diameter). Complex microvillous processes and ruffles were numerous on the surface of these cells and were observed surrounding extracellular melanosomes (Figs. 7b, c). Their cytoplasm contained large quantities of phagocytosed melanin within compound membrane-bound phagolysosomes (Figs. 7a, b, c). The large pale nucleus of the macrophage was eccentrically located and occasionally contained two nucleoli. Frequently the only identifiable cytoplasmic organelles apart from melanin were the Golgi apparatus (Fig. 7b) and some small swollen mitochondria; binucleate macrophages were occasionally observed (Fig. 7a). Lysis of

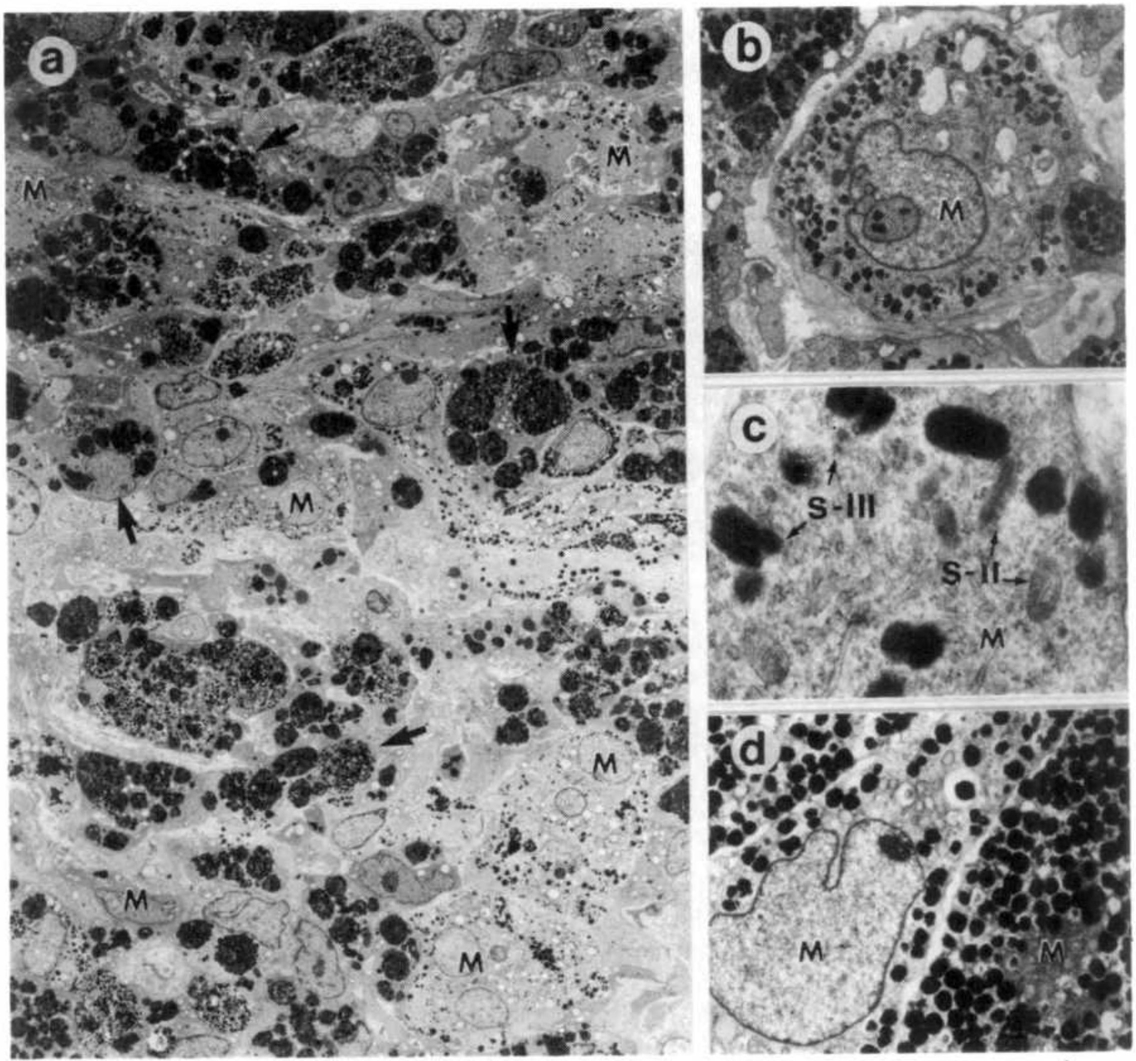

Fig. 4 *Electron micrographs of the ciliary body melanoma (block A_1) in a region where tumour cells were interspersed among macrophages.* (a) *Macrophages (arrows) are distinguishable, even at low magnifications, from the spindle melanoma cells owing to their large prominent complex melanophagolysosomes.* (b) *The variable appearance of the melanoma cells, particularly the stages of maturation of the melanosomes and the nuclear indentations. Note the banded appearance of the oval-shaped stage II and stage III premelanosomes in* (c) *in comparison with the more rounded, uniformly electron dense melanin granules in* (d). *Magnifications:* (a) ×*1400*, (b) ×*4000*, (c) ×*36 000*, (d) ×*3400*.

macrophages was observed as rupture of the cell membrane, which was lined internally by melanosomes. Melanin granules were extruded through the disrupted membrane (Fig. 8) and released into the anterior chamber and outflow system.

Those giant melanomacrophages which had penetrated into the trabecular meshwork had a more complex configuration, as they conformed to the intertrabecular spaces in the uveal, corneoscleral, and cribriform layers (Figs. 6a, 7a, 9a). In all the blocks the meshwork also contained melanoma cells and endogenous pigmented trabecular endothelial cells (TECs) (Fig. 9b). Melanoma cells were found either singly or in small aggregates and were present in reasonable numbers within the outflow tissues both close to and distant from the main tumour mass (Fig. 9b).

A large proportion of the melanin seen in the trabecular meshwork by light microscopy was found to be present within the TECs. The melanin granules

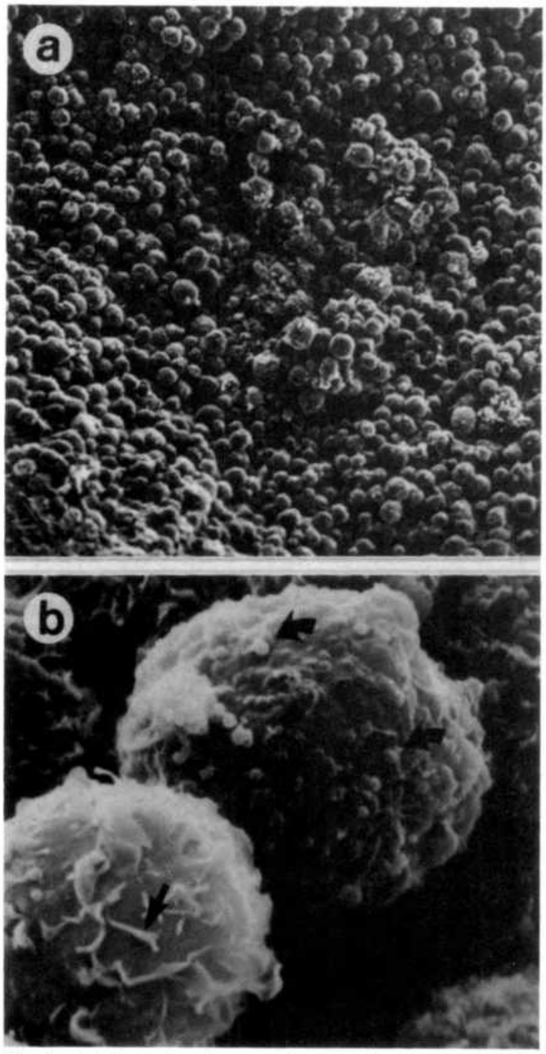

Fig. 5 (a) *Scanning electron micrograph of the anterior iris surface, which is carpeted by large numbers of rounded melanomacrophages.* (b) *higher magnification shows that some cells have the characteristic 'ruffled' plasma membrane of macrophages (straight arrow). Other cells have rounded granules, probably melanin, both on their cell surface (curved arrow) and directly beneath the plasma membrane, giving the cell a nodular appearance. Magnifications* (a) × *130,* (b) ×*2500.*

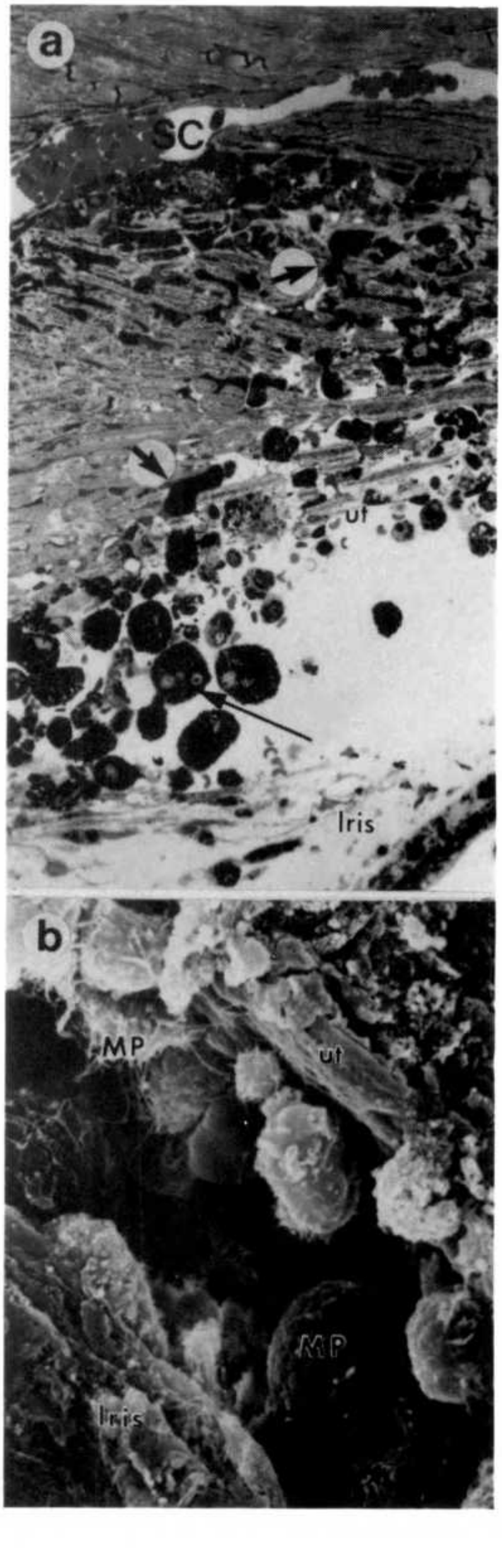

Fig. 6 (a) *Light micrograph (block D_3) and* (b) *SEM of the iridocorneal angle in the inferotemporal quadrant. Large numbers of giant melanomacrophages* (MP) *fill iridocorneal angle and obstruct the openings in the uveal meshwork as well as most of the intertrabecular spaces in the corneoscleral meshwork and cribriform layers. Note the globular appearance of these cells while still in the anterior chamber; however, they assume more complex shapes as they pass between the trabeculae (arrowheads). A binucleate macrophage is indicated (arrow).* SC=*Schlemm's canal,* ut=*uveal trabeculae. Magnifications:* (a) ×*300,* (b) ×*1000.*

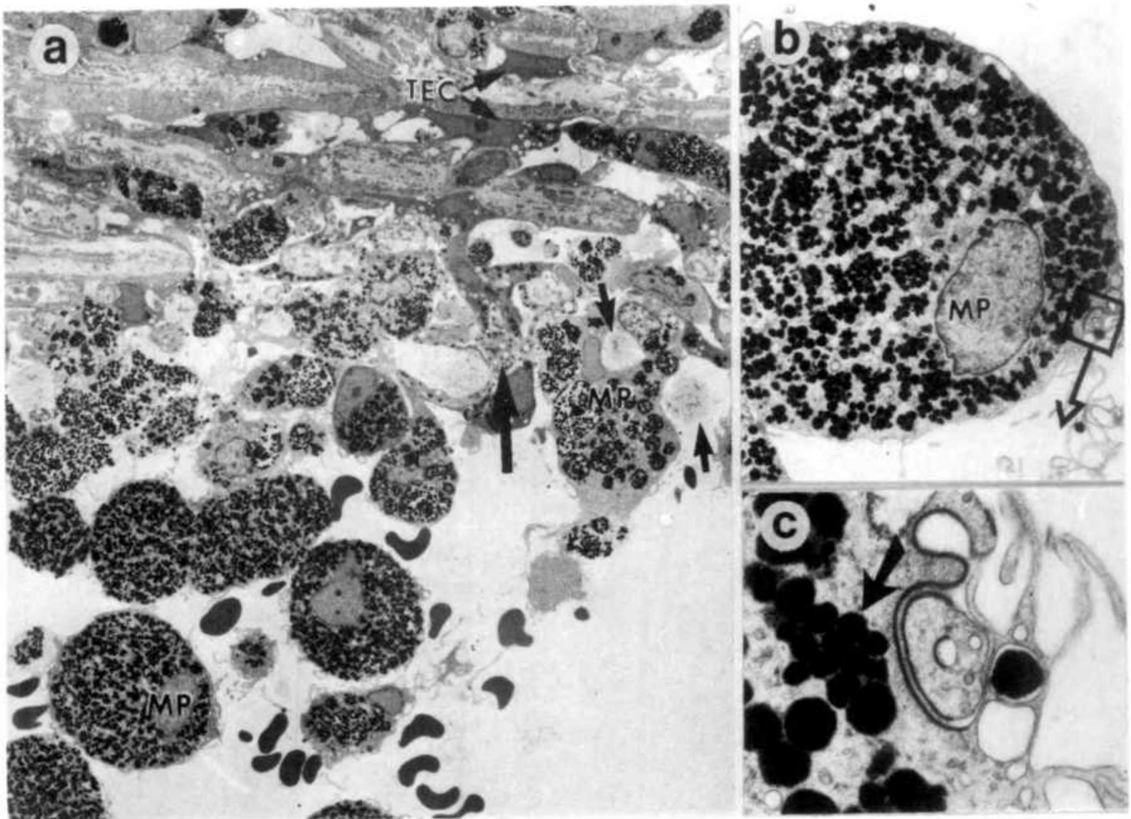

Fig. 7 *Electron micrographs of the giant melanomacrophages in the iridocorneal angle and uveal meshwork (block* D_3*).* (a) *Clearly illustrates the extent to which the openings in the uveal meshwork are obstructed. Some uveal trabeculae are denuded of TEC cover (small arrows). In some cases they are surrounded by macrophages* (MP) *or tumour cells (large arrow). Some TECs have prominent nucleoli.* (b) *and* (c) *Details of the melanin laden macrophages. Microvillous projections of the macrophages are clearly visible and at higher magnification appeared to be in the process of phagocytosing a free melanosome. An area of membrane specialisation whose function is unknown was associated with this area of the cell. Intracytoplasmic melanin is mostly within large complex membrane bound phagolysosomes (arrow) which contained stage III and mature melanosomes. Magnifications:* (a) ×*900,* (b) ×*2800,* (c) ×*15 000.*

were often lying singly in the cytoplasm, and pre- and mature melanosomes were identified (Figs. 10a, b). The majority of TECs were still in contact with the connective tissue cores and junctions with neighbouring TECs persisted (Fig. 10a). Some TECs showed signs of activation—that is, there were crenated nuclei, large prominent nucleoli, and in areas near the tumour the cytoplasm contained increased quantities of rough endoplasmic reticulum. The nuclear chromatin pattern resembled that of the tumour cells. However, few completely detached 'endothelial macrophages' were positively identified.

In regions close to the tumour and in the inferior quadrants, where the obstruction by macrophages and tumour cells was most marked, there were denuded and fused trabeculae (Fig. 9a). The connective tissue components of the trabeculae showed the normal morphological appearance of an eye in the sixth decade of life.

The TECs of the cribriform layer and to a less extent the lining endothelium of Schlemm's canal had also been active in phagocytosis of melanosomes (Fig. 10b). There was a paucity of giant vacuoles in the lining endothelium of Schlemm's canal, which is hardly surprising in view of the previous drainage procedure. The presence of red blood cells and plasma (Figs. 6a, 10b) in the lumen of the canal suggested that there had been a hypotensive situation in the anterior chamber at the time of fixation, causing a backflow of blood into Schlemm's canal.

There were some regions of Schlemm's canal especially close to the tumour which were closed by apposition of the inner and outer walls.

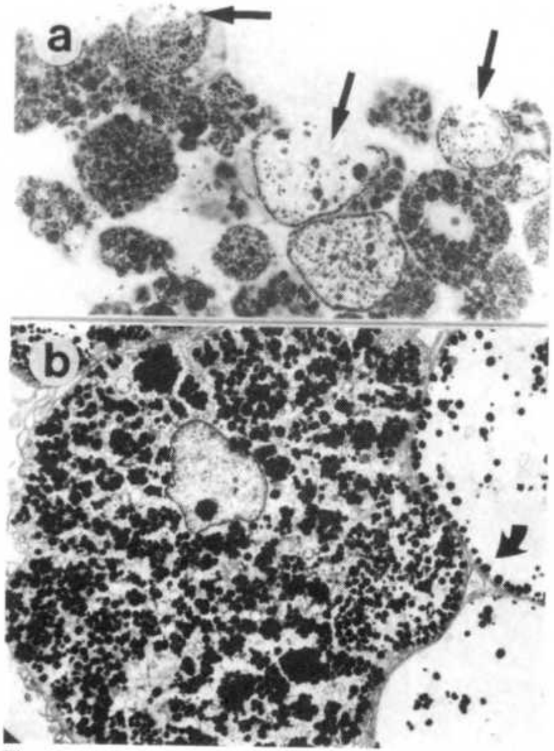

Fig. 8 *Light micrograph* (a) *and electron micrograph* (b) *of macrophage lysis in the chamber angle (block C_3). Melanin granules can be seen extruding from the ruptured plasma membranes in* (a) *(arrows). In* (b) *the shells of lysed cells are lined on their internal aspect by a few melanin granules (arrow). Magnifications:* (a) ×*700*, (b) ×*2000*.

Discussion

In general a raised intraocular pressure in a patient with an iris or ciliary body melanoma is a contraindication to conservative management, though many separate mechanisms may be responsible for the raised intraocular pressure in these cases.[1 6] If melanomalytic glaucoma is due only to blockage of trabecular tissue by macrophages engorged with melanin and not by tumour cells, treatment of the case by local surgical resection of the tumour may be justified. In the case reported here diagnostic trabeculectomy demonstrated the presence of viable tumour cells in the aqueous and in the angle remote from the tumour, indicating enucleation as the appropriate therapy. When a patient with a heavily pigmented ciliary body tumour presents with diffuse pigmentation of the iris and chamber angle, the following diagnoses should be considered—melanocytoma,[7] diffuse spread of malignant melanoma cells, or melanomalytic glaucoma.[1 2] Establishment of the diagnosis and assessment of the degree of tumour spread in such an eye might be aided by fine needle aspiration cytology or by biopsy, as in the present case. In either instance the identification of the various cell types may require routine paraffin histology to be supplemented by immunohistochemistry and electron microscopy. The present case provided an opportunity to document the morphological characteristics of the cellular infiltrate of the chamber angle in a case of melanomalytic glaucoma.

By conventional light microscopy the case bears many similarities to that described by Yanoff and Scheie[2] except for the fact that serial sections revealed small foci of surviving tumour cells. While a specific antimelanoma antibody for immunohistochemical studies is not yet available, the use of anti-S100 antibody revealed a positive reaction in some cells distant from the primary tumour site. This confirms the results obtained by electron microscopy and it supports the evidence of a previous immunohistochemical study.[8] The massive predominance of melanomacrophages, identified by conventional macrophage markers and electron microscopy, in the chamber angle and the trabecular meshwork, however, is consistent with the concept that aqueous outflow obstruction in this disease is simply a mechanical process.[2 3]

The giant melanomacrophages in the present case shared many of the characteristics of the type I clump cells (of Koganei),[9] namely cytoplasmic pseudopodia (or ruffles) around their circumference, lack of a basement membrane and cellular attachments, an eccentrically located nucleus, and an electron dense cytoplasm containing large complex melanophagolysosomes and lipid inclusions. These are not features of neuroepithelial cells, which were once thought to be the precursors of all clump cells. Greater than normal numbers of clump cells have been observed in pigmentary glaucoma,[10] though these authors considered some of them to be pigment epithelial in origin owing to the larger size of the melanosomes. However, it is possible that melanosomes, released from degenerating iris pigment epithelium, could have been phagocytosed by macrophages, which may as a consequence appear similar to activated pigment epithelial cells. An increase in clump cells was also observed in an experimental animal model of debris clearance from the iris and iridocorneal angle.[11] It seems therefore that macrophages are important to the clearance of released pigment in the anterior chamber, whether it originates from atrophy of the pigment epithelium or from a necrotic uveal melanoma. What is unclear is whether all these cells are derived from the resident population of histiocytic macrophages within the iris (clump cells) and trabecular meshwork or whether they are blood borne. In the present case it would seem from the numbers of macrophages involved in the response that they are most probably blood borne.

It is generally accepted that obstruction of the outflow pathways by macrophages is an important aetiological factor in many forms of secondary open angle glaucoma, including haemolytic, phacolytic,

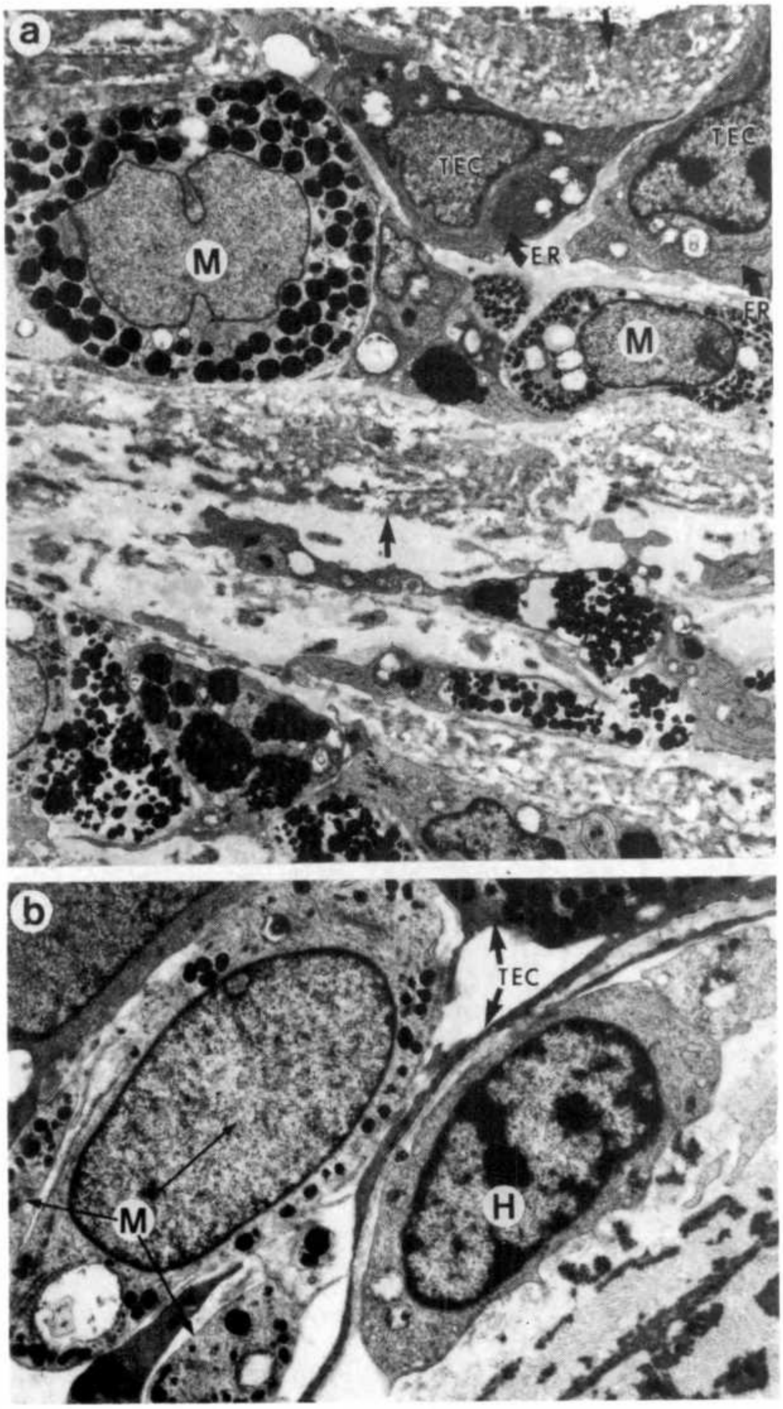

Fig. 9 *Electron micrographs of the corneoscleral meshwork at a site close to* (a) *block A_1, and remote from the main tumour mass* (b) *block D_3. In* (a) *note the variable morphological appearance of the melanoma cells* (M), *the fusion of adjacent denuded trabeculae, and the lack of intertrabecular spaces. Accumulations of long spacing collagen in the cortical zone of the trabeculae are evident (arrows). The TECs show some signs of activation, particularly increased quantities of rough endoplasmic reticulum* (ER). *In* (b) *note the presence of several melanoma cells* (M) *in the intertrabecular space. A mononuclear cell* (H), *probably histiocytic in nature, can be seen between the basement membrane of a TEC and the cortical zone of the trabeculae. Magnifications:* (a) ×*4000*, (b) ×*9000*.

and ghost cell glaucoma.[4,5] It seems likely from the absence of large quantities of free melanin in the tissues in the present case that outflow obstruction was due to cellular infiltration rather than an accumulation of particulate material.

The finding in the present and previous studies[3] of melanin phagocytosis by TECs clearly confirms the accepted view that these cells have a large phagocytic

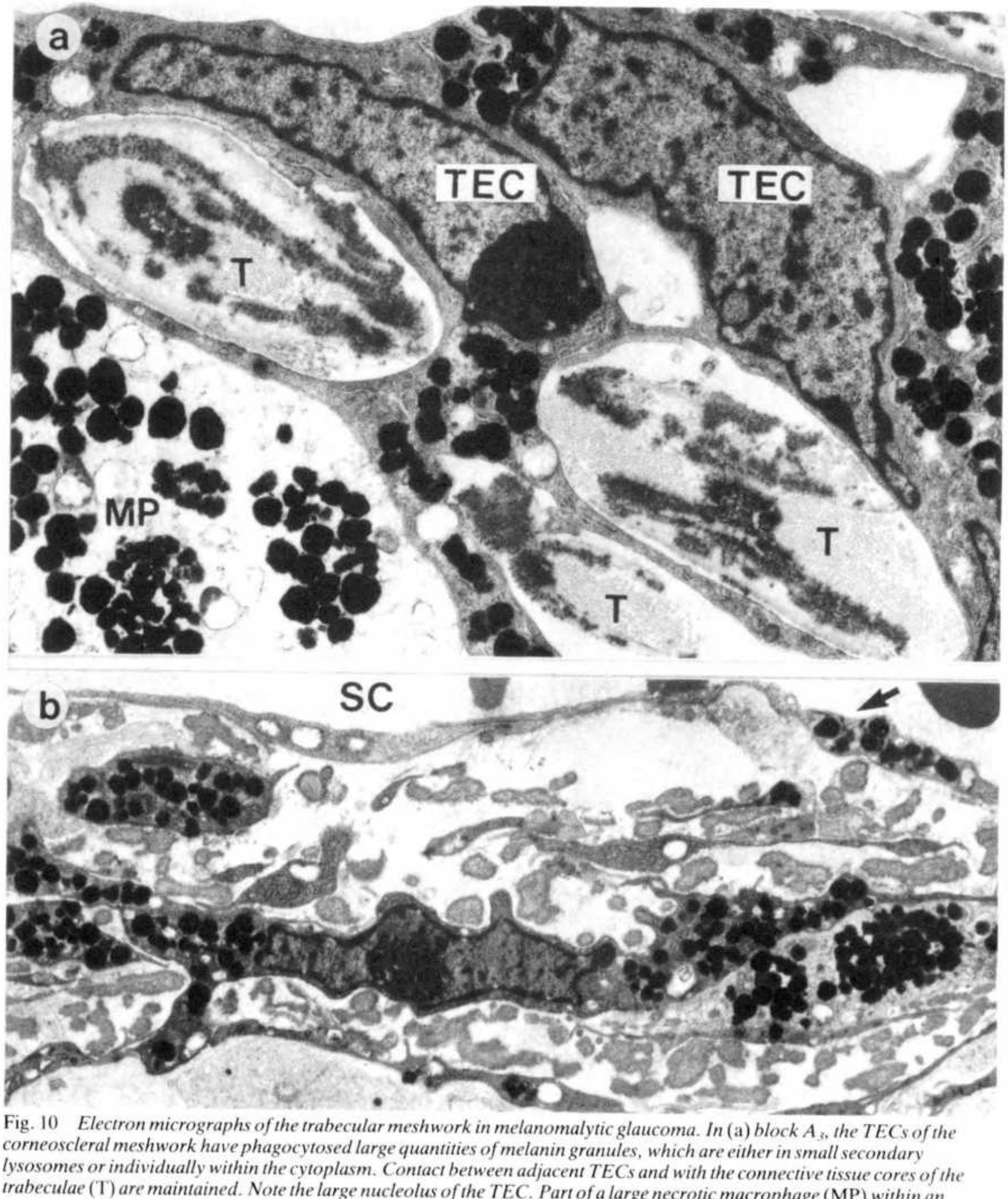

Fig. 10 *Electron micrographs of the trabecular meshwork in melanomalytic glaucoma. In* (a) *block A_3, the TECs of the corneoscleral meshwork have phagocytosed large quantities of melanin granules, which are either in small secondary lysosomes or individually within the cytoplasm. Contact between adjacent TECs and with the connective tissue cores of the trabeculae* (T) *are maintained. Note the large nucleolus of the TEC. Part of a large necrotic macrophage* (MP) *within an intertrabecular space is also visible.* (b) *Block D_3 illustrates the phagocytic capacity of TECs in the cribriform layer and the lining endothelium of Schlemm's canal (arrow). Again note the large nucleolus in the TEC. Magnifications:* (a) ×*10 288*, (b) ×*5621*.

capability which is essential to the function of the primate trabecular meshwork as a self-cleansing filter.[12] Melanin phagocytosis by TECs has also been observed in pigmentary glaucoma, a condition characterised by depigmentation of the iris stroma and epithelium associated with pigment dispersion in the anterior chamber.[10 13 14]

Evidence of TEC activation has been reported following traumatic hyphaema,[15 16] and it would seem likely that this would also occur in haemolytic and phacolytic glaucoma, though further ultrastructural studies of these conditions are required to confirm this suggestion. In the present case of melanomalytic glaucoma the TECs showed slight evidence of increased metabolic activity and protein synthesis, namely prominent nucleoi and Golgi apparatus and increased amounts of rough endoplasmic reticulum. It did not appear from the morphological evidence that many of the TECs had become totally detached from their trabeculae and neighbouring cells and assumed the role of mobile 'endothelial macrophages' which has been observed following exposure of the outflow tissues to haemorragic debris.[15 16] This may be due to differences in the character of the phagocytosed debris or the manner and length of exposure of the material to the cells of the trabecular meshwork. For example, in the present case the TECs may have only recently come into direct contact with free melanosomes as a result of macrophage lysis in situ. Van Buskirk and Leure-du Pree[3] did not observe such cell lysis in their investigation of melanomalytic glaucoma. The case studied by these authors differed from the present one in that the patient was only known to have had secondary open angle glaucoma for two weeks prior to enucleation, whereas in our case four months had elapsed since initial diagnosis of raised IOP. It seems possible, therefore, that macrophage lysis in situ may be a feature of the later stages of the disease. Although Van Buskirk and Leure-du Pree[3] observed 'endothelial macrophages,' they did state that there was difficulty in differentiating these from histiocytic macrophages.

The ultrastructure of TECs after activation approximates to those of tumour cells of low grade malignancy. The positive identification of melanoma cells within the trabecular meshwork at sites in the circumference of the chamber angle distant from the tumour mass is an important finding of the present study which has not been reported in previous studies.[2 3] In the present case it seems unlikely that these cells had a role in obstruction of the aqueous pathways. However, melanoma cells in the outflow system may increase the risk of metastatic spread. Shields and Klintworth,[17] in a histological study of 11 cases of anterior uveal melanomas, found some evidence of tumour cell infiltration of the iridocorneal angle in six, of which four also had raised IOPs. The mechanism of the glaucoma in their cases was secondary to direct tumour invasion of the outflow system and did not appear to be melanomalytic, though they positively identified melanin laden macrophages in the angle of three cases.

It is obvious that the outflow pathways present a possible route for tumour cells to enter the general circulation, and Shields and Klintworth[17] have emphasised that indeed increased IOP may accelerate the extraocular spread of cells. They observed that three out of the four fatalities had glaucoma associated with their ciliary body melanomas. It is clear from our findings that tumour cells may be present in the angle distant from the tumour in melanomalytic glaucoma and may therefore be an important factor in the management of such cases.

We thank Professor W S Foulds for his kind co-operation with the study of this case. We are grateful to Mrs C Morris for artistic help and to Miss B Robinson and Mrs L Peedle for secretarial assistance.

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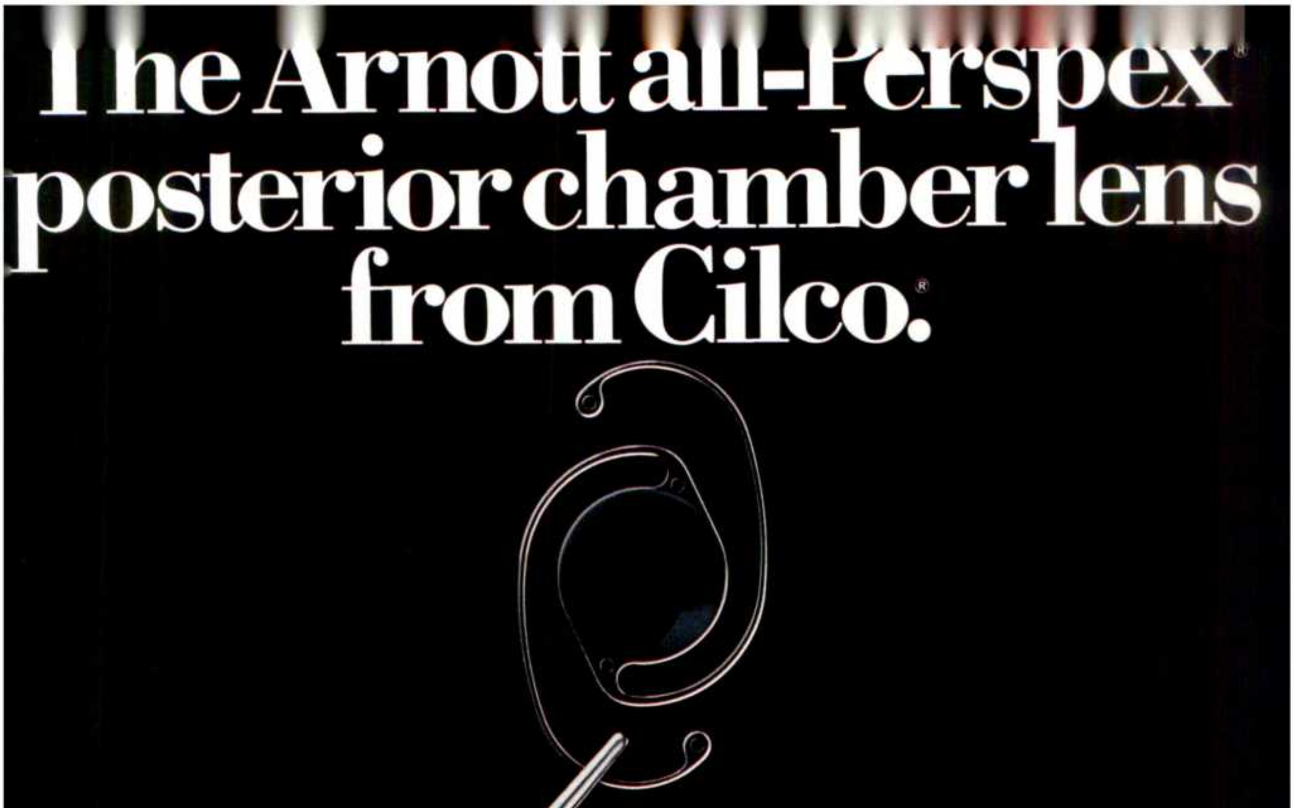

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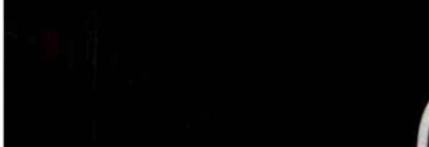

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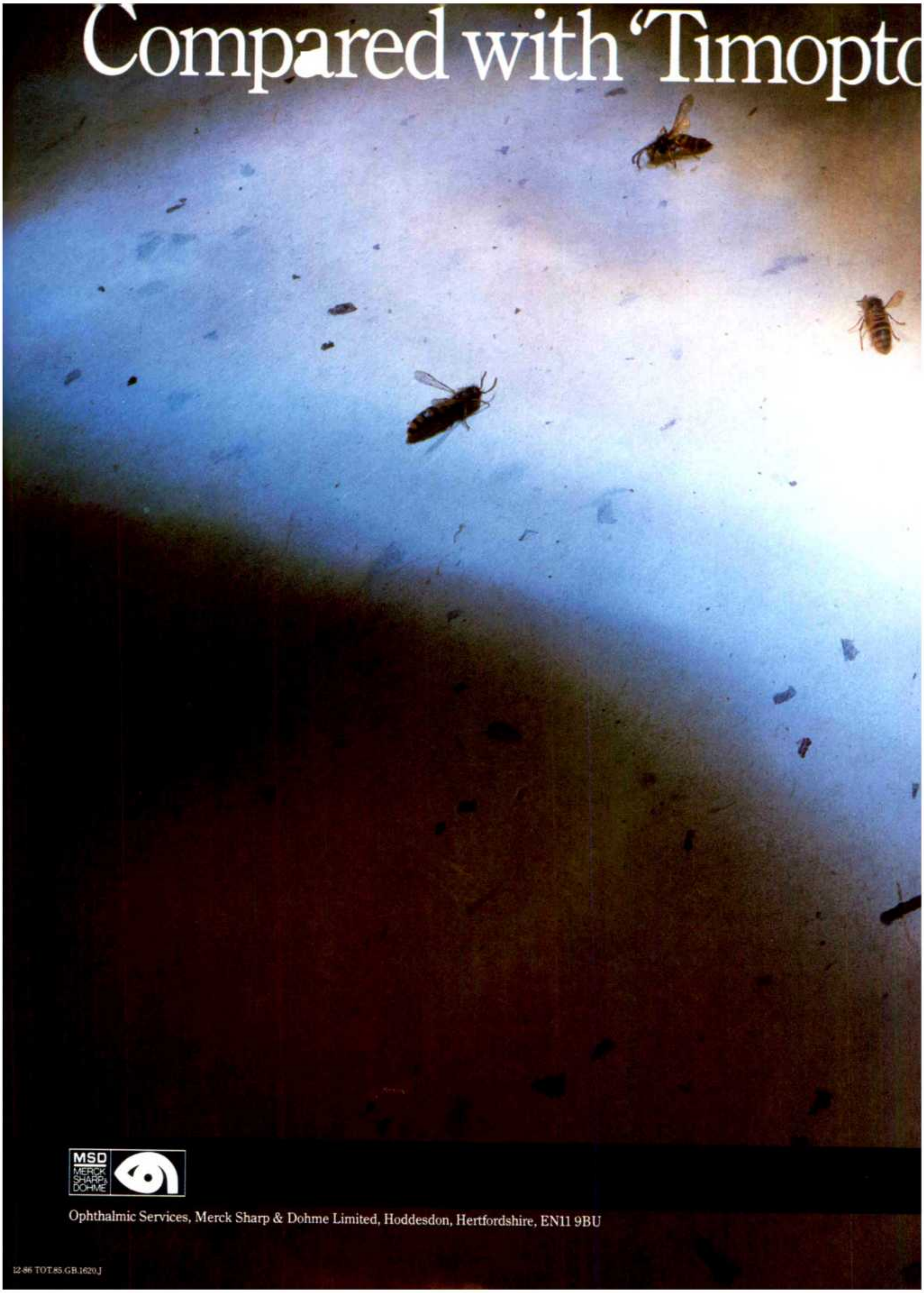

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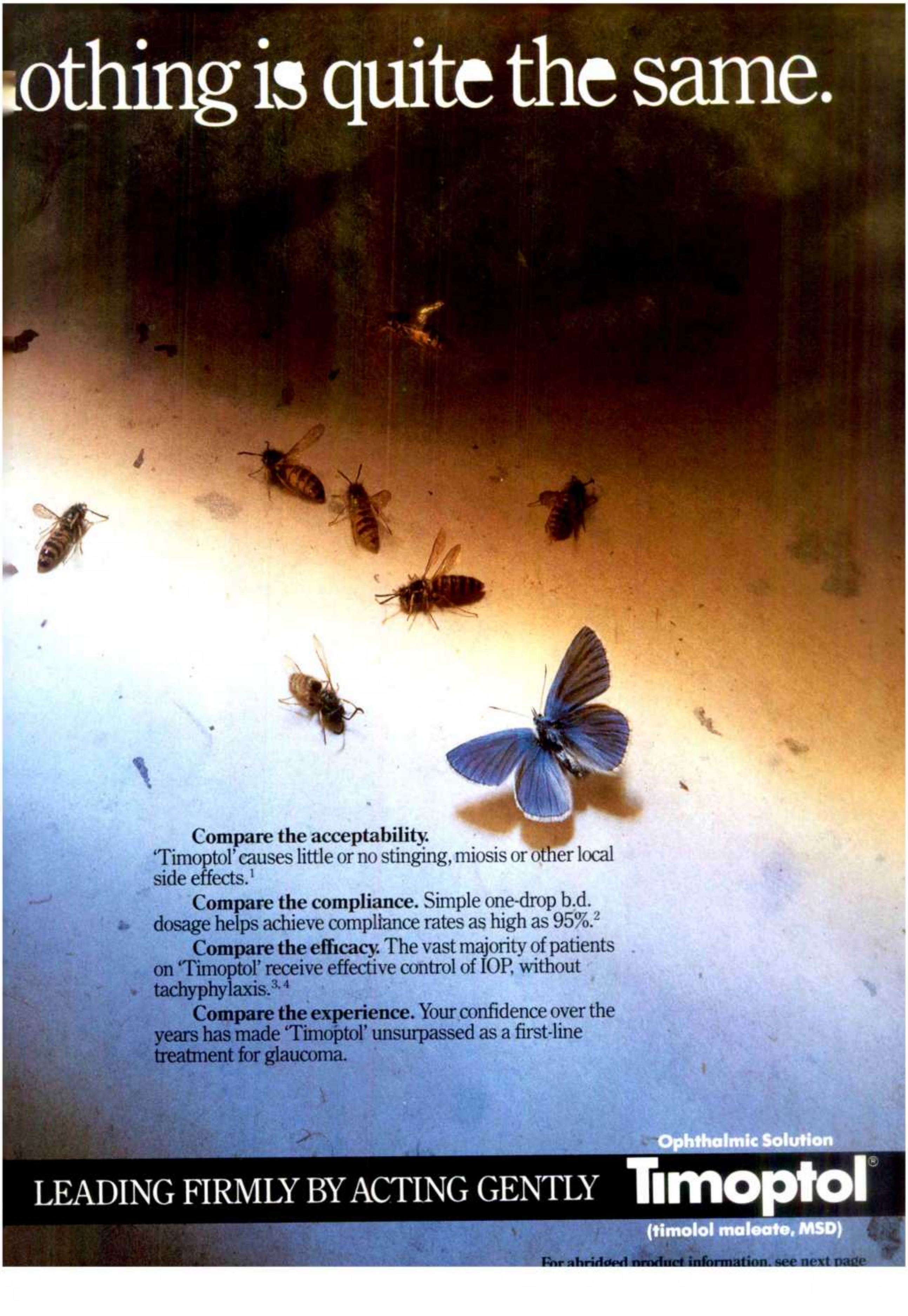

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British Journal of Ophthalmology, 1986, **70**, 907–910

Desmoplastic malignant melanoma masquerading as chalazion

J P ROPER, T JONES, AND J D A COMMON

From the Department of Ophthalmology, North Staffordshire Royal Infirmary, Stoke on Trent

SUMMARY Desmoplastic malignant melanoma is a rare and highly malignant tumour, which usually occurs in the head and neck. This is demonstrated by a case history of a patient with this lesion on the lower lid, which has not been previously described in the British ophthalmological literature. The lesion often presents considerable problems of histological diagnosis.

A 77-year-old man was referred by his doctor with a history of a sore left lower eyelid and an area of ulceration which had been present for four months at the time of referral. He had a history of right retinal detachment operations 10 and 11 years previously. On examination his corrected visual acuities were counting fingers on the right and 6/18 on the left. The intraocular tensions were raised, at 32 mmHg on the right and 45 mmHg on the left. The optic discs showed glaucomatous cupping. The left lower eyelid showed an area of ulceration at the junction of the medial and middle thirds, which clinically was thought to be a basal cell carcinoma.

He was prescribed 0·5% timolol maleate drops twice daily for his glaucoma, and it was planned to excise the presumed basal cell carcinoma under local anaesthetic as a day case. It was thought that the lesion could easily be excised by a one-third wedge excision and it was not photographed.

When he was admitted three weeks later, the lesion on the lid margin had extended, and a 50% excision would be necessary to achieve complete clearance with a 1–2 mm margin on either side of the lesion. One half of the left lower lid was removed by wedge excision and the lower lid reconstructed by division of the lateral canthal ligament and flap advancement. The excised specimen was sent for histological examination. The lid made a satisfactory recovery and healed well.

The initial histological diagnosis was reported as follows: 'Lower eyelid 1·5×1·0 cm, with a pale raised smooth surfaced lesion 0·8×0·5 cm. at the junction of the two epithelial surfaces. *Microscopy*. The lesion consists of interlacing bundles of cellular fibrous tissue with interlacing bundles of cellular fibrous tissue and overlying ulceration. Degenerating eosinophil muscle fibres are present within the tumour which contains multinucleate giant cells. The appearances are of a chalazion.'

The histological diagnosis was considered incompatible with the clinical appearance of the lid, and re-examination of the slides was requested. The result was that the diagnosis was revised to that of desmoplastic malignant melanoma.

PATHOLOGY

Light microscopy (Figs. 1–3)

The specimen was fixed in neutral buffered formalin and mounted in paraffin. Routine haematoxylin and eosin stain showed an ulcerating mass situated within the epidermis, consisting of atypical spindle cells with occasional larger epithelioid cells near the surface. This extended into basal epidermis at the edge. Mitotic figures were frequent, with up to four per high field. The overlying epidermis was largely lost owing to ulceration. No pigment was present either within the neoplasm itself or in the adjacent intact epidermis. Masson's trichrome stain showed the presence of abundant collagen within the lesion; reticulin stains showed whorls of spindle cells with outlining of epithelioid cells. The Masson-Fontana stain for melanin was negative.

Electron microscopy (Fig. 4)

Pieces of neoplasm were part-fixed in osmium tetroxide and processed for electron microscopy. Sections were then examined with an AEI Corinth 500 electron microscope, which confirmed the presence of nuclear pleomorphism and abundant

Correspondence to Mr J D A Common, Ophthalmology Department, North Staffordshire Royal Infirmary, Stoke-on-Trent.

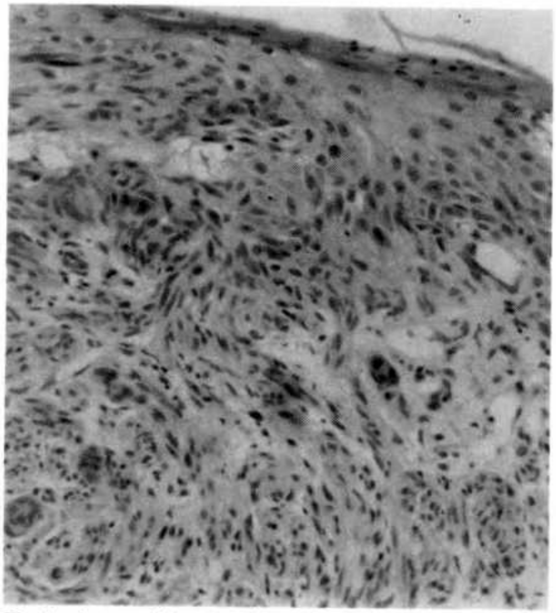

Fig. 1 *Intact epidermis with underlying spindle cell elements extending into the junctional zone. Haematoxylin and eosin.*

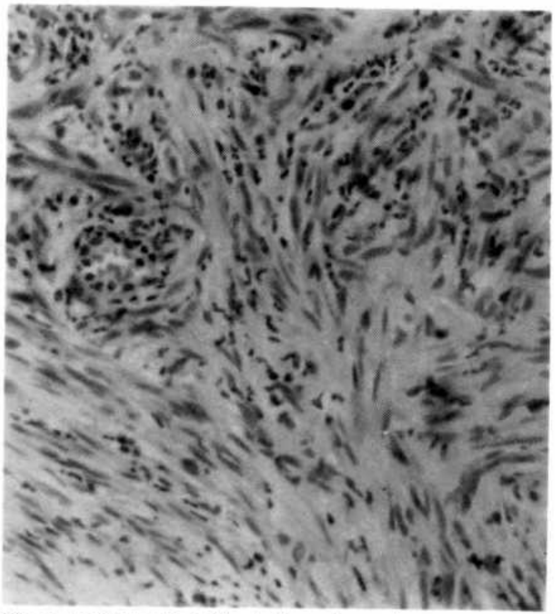

Fig. 2 *Spindle cells infiltrated by polymorphs. Haematoxylin and eosin.*

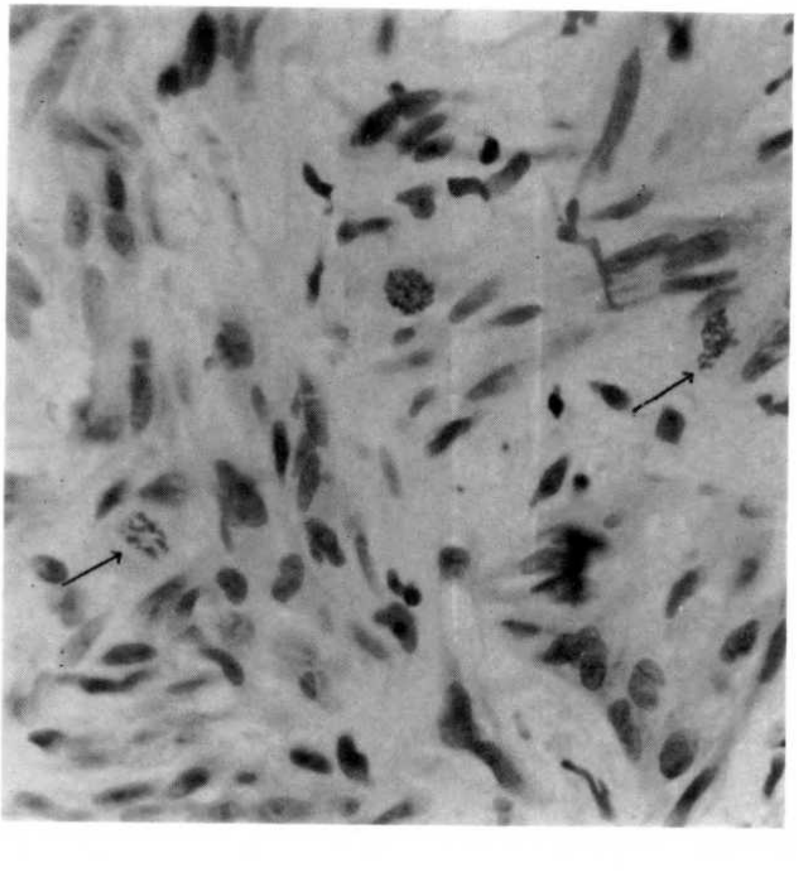

Fig. 3 *High power view showing frequent mitotic figures amid spindle cells with large nuclei. Haematoxylin and eosin.*

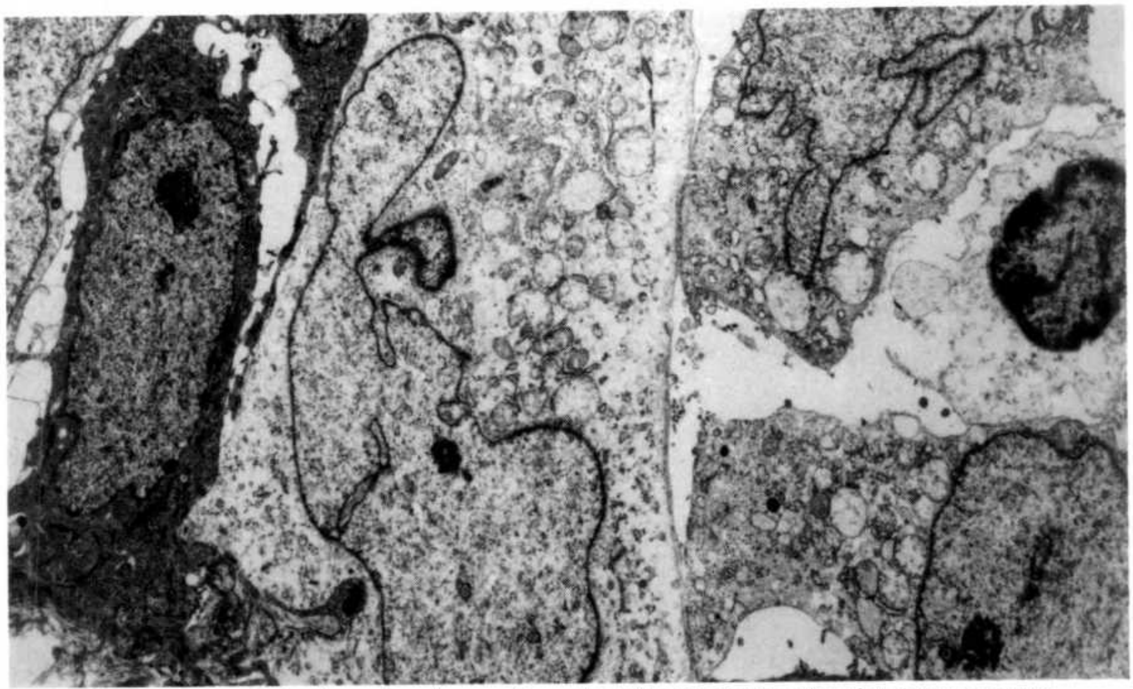

Fig. 4 *Electron micrograph showing nuclear pleomorphism and swollen mitochoniria. No melanosomes are present. (×3560).*

collagen. No melanosomes or premelanosomes were seen. Precollagen fibrils were not present in the cytoplasm. However, many of the cells contained dilated rough endoplasmic reticulum. The features were consistent with those of desmoplastic melanoma.

Immunoperoxidase studies

These were performed by the standard peroxidase-antiperoxidase technique on formalin-fixed, paraffin-embedded tissue. Monoclonal antibody was applied against S100, a protein present in cells of neural origin, which stained the cytoplasm and nuclei of the spindle cells throughout the neoplasm, but particularly near the surface, suggesting the diagnosis of desmoplastic malignant melanoma.[1 2]

Discussion

In 1971 Conley *et al.* reported on seven cases in which inconspicuous, superficial, melanotic lesions resulted in bulky subcutaneous tumefactions, mainly in the head and neck. Clinically and histologically they appeared as locally invasive fibrous tumours, but the elongated neoplastic cells differed cytologically from neoplastic fibroblasts and behaved as highly malignant, recurring, and metastasising neoplasms. Some recurrences and metastases were histologically malignant melanomas. This clinicopathological entity was termed 'desmoplastic malignant melanoma.'[3]

These patients were between 13 and 80 years of age, most being over 40. The original red or brown lesions were flat and insignificant except one with a subcutaneous nodule. These clinically innocuous lesions were not thought to be definitely malignant initially, and in those treated by excision rather than fulguration the pathological diagnosis was very varied. Subsequently hard, subcutaneous, nodular tumours of fibrous appearance developed from six months to two years later. These recurred after excision, and metastases developed in regional lymph nodes. Visceral secondary tumours usually followed.

The total reported cases to date are 16, nearly all from the United States,[4] and the first British report was in 1982.[5] 70% of cases have occurred in the head and neck. In 1982 a case of desmoplastic malignant melanoma of the upper eyelid was described. This case presented as a small pigmented lesion on the palpebral conjunctiva, which had previously been incised and curetted. Radiological examination showed demineralisation of the orbital margin. At excision there was extension of the tumour in the superior orbit. Multiple orbital recurrences followed, and two courses of radiation were ineffective.

Table 1 *Histological diagnoses in some cases eventually described as desmoplastic malignant melanoma*

Initial histological diagnosis	*Histology of recurrent lesions*
1. Low grade malignant tumour of undermined type	Squamous cell carcinoma, fibrosarcoma
2. No biopsy	Fibrous tissue hyperplasia, cheloid fibroma, hypertrophied scar, fibromatosis
3. Lentigo naevus	Superficial malignant melanoma with dense scar
4. Superficial malignant melanoma	Chronic inflammation, spindle cell tumour, reactive hyperplasia, fibrosarcoma, hyperplastic scar
5. Blue naevus	Fibromatosis
6. No biopsy	Lentigo maligna
7. Reactive hyperplasia	Malignant melanoma
8. Lentigo maligna	Scar tissue, spindle cell neoplasm
9. Epithelioma	
10. Neurofibrosarcoma	
11. Lipogranuloma	
12. Chalazion	

Pulmonary and central nervous system metastases caused the death of the patient. This was the only recorded case arising from a mucosal rather than a cutaneous lesion.[4]

The outstanding feature of previous cases was their extreme malignancy. Of the previous cases in which follow-up after radical excision is recorded only one remained clear of the disease, and this was after only one year.[7] The average survival from presentation was 21 months.

We believe that the case reported here is the first in the British ophthalmological literature, and is typical in every respect. It is only the second reported case involving the ocular adnexa. The nature of the spindle cell component has not been defined, despite special stains and electron microscopy. It has been suggested that the origins may be melanocytic, fibroblastic, neural, or histiocytic. The problem in establishing the origin of the cells lies partly in interpreting the desmoplastic reaction.[8] Reactive desmoplastic responses have been recorded in squamous cell carcinoma and in cases of traumatic and actinic damage.[9-11]

Despite the uncertainty of the cellular origin desmoplastic malignant melanoma is a definite clinical entity, whose early recognition is of paramount importance. Because of the undifferentiated nature of the spindle cell component, careful correlation of the clinical findings is necessary to establish the correct diagnosis. If the entire lesion is not removed, early local recurrences and widespread metastases will result. Table 1 demonstrates the difficulty of histological diagnosis in some cases which were finally diagnosed as desmoplastic malignant melanoma.

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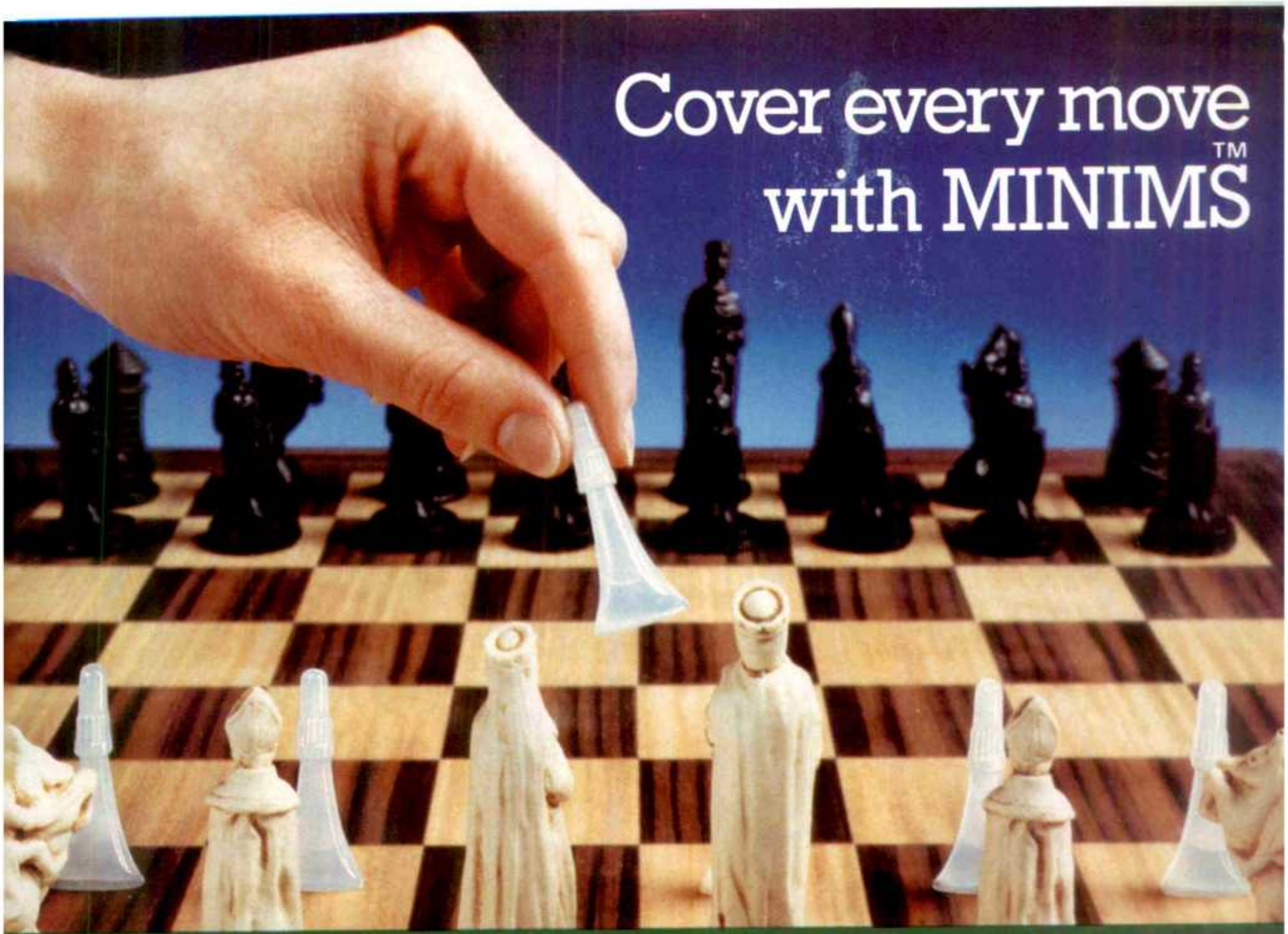

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LACRI-LUBE *Presentation:* Sterile, bland, non-medicated ointment for topical administration to humans, containing white petrolatum mineral oil, non-ionic lanolin derivatives with chlorobutanol 0.5% as a preservative. *Uses:* Useful as adjunctive therapy to lubricate and protect the eye in conditions characterised by exposive keratitis, decreased corneal sensitivity, recurrent corneal erosions, and keratitis sicca. *Dosage and Administration:* For topical administration. Pull lower lid down to form pocket. Apply small amount as needed. *Contra-indications, etc:* No known contra-indications. *Pharmaceutical precautions:* Store away from heat. To avoid contamination during use, do not touch tip to any surface. *Legal Category:* P. *Package Quantities:* Available in 3.5g ophthalmic tubes. Basic NHS cost (as at January 1984)

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Extended retinal tamponade in the treatment of retinal detachment with proliferative vitreoretinopathy

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SUMMARY We have used intraocular sulphur hexafluoride or liquid silicone as an adjunct to vitreous surgery in the treatment of a non-randomised sequential series of 19 eyes with retinal detachment complicated by proliferative vitreoretinopathy. We have studied the surgical results and complications of these two tamponades and drawn preliminary conclusions on their use in retinal reattachment surgery. After a seven-month minimum follow-up 13 (68%) of the eyes have reattached retinas. Six (60%) of 10 eyes treated only with silicone have reattached retinas, and four (67%) of six eyes treated only with sulphur hexafluoride gas tamponade have reattached retinas. An additional three eyes treated initially with silicone oil subsequently developed retinal detachments; all were successfully reattached with sulphur hexafluoride tamponade after silicone oil removal. Intraoperative pneumatic retinal reattachment to assess relief of retinal traction combined with the production of widespread chorioretinal adhesions to wall off persistent anterior traction and detachment, as well as extended postoperative gas tamponade of the retina, appears to enhance the surgical results in retinal detachment complicated by proliferative vitreoretinopathy. Silicone oil tamponade of the retina appears to be useful in cases where retinal traction cannot be entirely relieved and in patients who are unable to tolerate the head positioning required for effective gas tamponade of the retina. A controlled clinical study recently begun will be required to define further the precise role of these methods of retinal tamponade.

Proliferative vitreoretinopathy (PVR) is the commonest cause of failure in retinal reattachment surgery, occurring in 5–10% of cases of retinal detachment[1] and accounting for irreparable loss of vision in approximately 1000 eyes in the United States each year.[2] The proliferation of retinal pigment epithelial cells and glial cells on tissue surfaces within the eye, which is the hallmark of this disease,[3 4] can present differing configurations of retinal detachment with differing surgical complexity, depending on the extent of involvement of the preretinal and subretinal surfaces, posterior vitreous face, and vitreous base.

Surgical techniques for the repair of these complex detachments have included scleral buckling,[5-7] liquid silicone,[8-10] and vitrectomy in combination with a variety of techniques. These include membrane dissection and intraocular gas tamponade,[11] intraocular liquid silicone tamponade,[12-14] and endolaser photocoagulation.[15] The evaluation and interpretation of surgical results with these different surgical techniques has been hampered by the lack of a uniform description of the type and complexity of the retinal detachments as well as the different surgical techniques that have been used.

We report the surgical results and complications of a non-randomised, sequential series of 19 eyes with proliferative vitreoretinopathy treated by vitreous surgery techniques combined with extended intraocular sulphur hexafluoride gas tamponade or liquid silicone tamponade.

Materials and methods

We reviewed the records of 19 consecutive patients (19 eyes) with retinal detachment complicated by proliferative vitreoretinopathy operated on by us from April 1983 to March 1984, with a minimum

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follow-up of seven months and a maximum follow-up of 20 months (average 11 months). There were 16 males and three females, with a mean age of 44 years. There were nine right eyes and 10 left eyes. Four of the patients were completely blind in the fellow eye. Thirteen (68%) of the eyes were aphakic, five (26%) of the eyes were phakic, and one (5%) was pseudophakic. Eighteen (95%) of the eyes had undergone previous scleral buckling and 12 (65%) of the eyes had undergone previous vitrectomy surgery. Penetrating trauma was the cause of retinal detachment in three (16%) of the eyes.

Eyes were graded preoperatively according to the Retina Society classification.[16] A dense cataract allowed intraoperative classification only in one eye. The retinal detachment and vitreous anatomy were recorded with a retinal drawing, Tolentino cross-sectional drawings, and 60° fundus photographs. No pre-existing retinal breaks were identified preoperatively and intraoperatively in six (32%) eyes. One break was identified in five (26%) eyes, two breaks were identified in three (16%) eyes, and three or more breaks were identified in five (26%) eyes.

All eyes were operated on by one of us (WHS) in conjunction with other members of the Retinal Faculty at the University of California, San Francisco. A lensectomy was performed in four of the five phakic cases. In one eye in which silicone was used the clear lens was left in place. A pars plana vitrectomy was performed in all cases, including eyes that had previously undergone vitrectomy surgery, to relieve vitreoretinal traction and allow access to the retinal surface. Preretinal membranes were dissected and removed with forceps, and star folds were carefully opened when possible. Anterior folding of the retina towards the ora serrata (anterior loop contraction) was relieved by vitrectomy removal of as much of the residual vitreous base as possible followed by blunt separation of the anterior loop of the retina. In one eye a 90° peripheral circumferential retinotomy was performed to relieve anterior loop contraction.

Subretinal fibrosis in four patients causing retinal elevation through the macula was treated by retinotomy followed by sectioning of the subretinal band. In two of these four patients with extensive subretinal fibrosis, peripheral relaxing or posterior relaxing retinotomies were performed.

Subretinal fluid was drained internally in 16 of the 19 eyes through a pre-existing break or intentional retinotomy on the superonasal side of the optic nerve. In three eyes with focal areas of retinal contraction, all of which had undergone previous vitrectomy surgery, a preoperative fluid-gas exchange was performed to achieve absorption of the subretinal fluid.

Of those cases tamponaded with silicone a silicone-air exchange was performed in eight and a silicone-fluid exchange was performed in the remaining five. Dow-Corning medical grade 1000 centistoke liquid silicone was injected with an automated pneumatic pump either through the pars plana infusion terminal or through a 20-gauge needle placed through the peripheral cornea while either the intraocular air or fluid was simultaneously aspirated.

In those cases receiving sulphur hexafluoride gas the air filled eye was perfused with 30 ml of a 20% sulphur hexafluoride-air mixture through the infusion canula at the completion of the vitrectomy, with air exiting passively through an open sclerotomy.

Revision of the pre-existing scleral buckle was done in seven eyes. No revision was required in 11 eyes and a primary scleral buckle was performed in one eye. A broad high scleral buckle was obtained with a No. 279 solid grooved silicone implant or a 7·5 mm silicone sponge anchored to the sclera with two mattress sutures in each quadrant. Retinal breaks were treated either with argon laser endophotocoagulation or transscleral cryotherapy. Intraoperative endophotocoagulation of the retina overlying the scleral buckle, regardless of the identification of a retinal break, was performed 360° in two eyes. Supplemental postoperative argon blue-green laser photocoagulation of the retina overlying the scleral buckle was performed in 11 eyes. A scatter photocoagulation pattern over the inferior retina was used in three patients with silicone tamponade.

Postoperative fluid-gas exchange with 20% to 60% sulphur hexafluoride gas (depending on the volume to be exchanged) was performed in all six gas filled eyes. In addition the retina in three silicone filled eyes redetached, and these eyes were treated by removal of silicone oil and replacement with sulphur hexafluoride gas tamponade. These eyes also required postoperative fluid-gas exchanges. The gas tamponade was maintained at 50% or greater of the intraocular volume for 14 to 21 days.

Silicone oil was removed from two eyes with reattached retinas and replaced with balanced salt solution. Silicone oil was not removed in the remaining five patients with reattached retinas owing to the patient's refusal to undergo further surgery as well as the anxiety of both patient and physician about a recurrent retinal detachment.

Retinal reattachment was defined as reattachment of the retina posterior to the scleral buckle.

Results

Thirteen (68%) of the 19 eyes were successfully reattached, with a seven to 20-month follow-up period (average 11 months). Of these 13 eyes six (46%) were successfully reattached with a single operation and seven (54%) were successfully reattached with two or more operations (Table 1).

The PVR anatomic classification versus the retinal reattachment rate is summarised in Table 2.

Visual acuity results are summarised in Table 3.

Silicone oil was removed three months postoperatively from one eye with a reattached retina. This eye developed a recurrent retinal detachment that was not reoperated on. An additional eye underwent silicone oil removal six months after surgery, with the retina remaining attached.

INTRAOPERATIVE COMPLICATIONS

An unplanned retinal break occurred during membrane dissection in five (26%) of 19 eyes.

In one eye extensive napkin ring subretinal fibrosis prevented retinal reattachment. Subretinal migration of silicone oil occurred in this patient owing to inadequate relief of retinal traction.

Table 1 *Reoperations for recurrent retinal detachment*

	No. eyes	*Reattached*			
		Total (%)	*One operation*	*Two operations*	*Three operations*
Silicone only	10	6 (60)	4	2	–
Gas only	6	4 (67)	2	2	–
Silicone followed by gas	3	3 (100)	–	2	1
Total	19	13 (68)	6	6	1

Table 2 *Retinal reattachment rate and severity of PVR*

Grade PVR	*No. of eyes*	*No. (%) reattached*
C1	1	0 (0)
C3	4	3 (75)
D1	3	3 (100)
D2	5	4 (80)
D3	6	3 (50)

Table 3 *Final visual acuity in 13 cases with reattached retinas*

Visual acuity	*No. eyes*		
	With silicone	*With gas*	*With silicone and gas*
20/100	1		
5/200	1		2
4/200	–	1	
2/200	2	1	
HM	2	2	
LP	–	–	1

HM=hand movements. LP=light perception.

POSTOPERATIVE COMPLICATIONS

Postoperative complications in 17 eyes with intraoperative retinal reattachment are listed in Table 4.

Recurrent proliferative vitreoretinopathy occurred in 12 (71%) of 17 eyes successfully reattached at the time of surgery (Table 5).

Recurrent retinal detachment posterior to the scleral buckle occurred 11 times in 10 eyes (Table 4). No retinal breaks were identified in six (60%) eyes. Old retinal breaks that had reopened were identified in three (30%) eyes. New retinal breaks were identified in two (20%) eyes. Within the group of 11 eyes in which the retina redetached recurrent proliferative vitreoretinopathy was noted in eight (73%).

In six eyes treated initially with silicone the retina redetached, and all underwent reoperation with addition of silicone or replacement of silicone with gas. Five of these six eyes continued to remain attached.

Of the four eyes that were treated with gas tamponade initially in which the retina redetached, two were reoperated on. Anterior loop contraction was present in both eyes. No breaks were identified in either eye. A fluid-gas exchange resulted in retinal reattachment in both cases and was followed by extensive laser photocoagulation of the retina 360°

Table 4 *Postoperative complications in 17 eyes with intraoperative retinal reattachment*

	No. eyes		
	With silicone (8)	*With gas (6)*	*With silicone and gas (3)*
Recurrent proliferation	3	6	3
Recurrent retinal detachment	6	4	1
Angle closure glaucoma	2	–	–
Emulsification of silicone	1	–	–
Corneal decompensation	3	–	–
Hypotony	–	1	–
Fibrin pupillary membrane	1	1	–

Table 5 *Recurrent proliferative vitreoretinopathy in 17 eyes with intraoperative retinal reattachment*

	No. eyes		
	With silicone (8)	*With gas (6)*	*With silicone and gas (3)*
Focal contraction (macular pucker or extramacular starfold)	1	2	3
Anterior loop contraction only	1	1	–
Combination focal and anterior loop contraction	–	1	–
Widespread epiretinal membranes	1	2	–
Total no. eyes with recurrent PVR	3	6	3

over the scleral buckle. The retina remained attached posterior to the scleral buckle, though residual fluid anterior to the scleral buckle is present in both cases.

Angle closure glaucoma occurred in one aphakic eye and one pseudophakic eye filled with silicone. Neither eye had a peripheral iridectomy performed at the time of surgery. The aphakic angle closure glaucoma was managed by performing an inferior peripheral iridectomy. The pseudophakic pupillary block was treated by first attempting a laser iridotomy nasally, which was unsuccessful in breaking the pupillary block, and later successfully treated by constricting the pupil with a topical miotic.

Emulsification of silicone in the anterior chamber without increase of intraocular pressure was observed in one patient three months after intraocular silicone injection. The silicone was removed uneventfully six months after injection and the eye continued to maintain a normal intraocular pressure and a reattached retina.

Silicone was not removed in five eyes with reattached retinas. Complications occurred in three of these five eyes and were limited to the cornea. Corneal oedema occurred in one eye and a linear subepithelial band opacity occurred in two eyes associated with corneal-silicone touch.

Neither the pseudophakic nor aphakic eyes with retained silicone developed sustained elevated intraocular pressure.

No complications were noted from intraocular gas injection.

ANALYSIS OF FAILURES

Inadequate relief of subretinal fibrosis contraction in one eye and epiretinal membrane contraction in another eye prevented intraoperative retinal reattachment in two of the six failed cases.

Widespread reproliferation of epiretinal membranes occurred in two eyes treated by extended gas tamponade and was associated with recurrent retinal detachment.

One eye developed an inferior retinal detachment under silicone oil after an extensive inferior retinotomy for release of subretinal fibrosis traction and was not reoperated on.

In one eye the retina redetached after removal of silicone oil.

Of the six failures, the preoperative Retina Society classification was C1 (one eye), C3 (one eye), D2 (one eye) and D3 (three eyes).

Discussion

Intraocular gas has occupied an increasingly important role in the treatment of retinal detachment since Rosengren[17] described the use of air to tamponade retinal breaks and Norton[18] described the use of sulphur hexafluoride to extend the intraocular gas tamponade. Cibis *et al.*[8] and later Scott[9] described an added dimension to the role of intraocular tamponades in retinal detachment with the use of liquid silicone to tamponade retinal breaks as well as to dissect epiretinal membranes.

The introduction of vitrectomy surgery and membrane dissection techniques by Machemer *et al.*[3] and, later, the addition of retinotomy techniques by Machemer[19] and Zivojnovic *et al.*[13] have encouraged the use of long-lasting internal tamponades not only to close breaks formed by vitreous traction and contractile cellular membranes, but also to close iatrogenic retinal breaks or retinotomies created at the time of vitreous surgery. Vitreous surgery techniques have, in addition, encouraged the use of vitreous substitutes such as liquid silicone and air to allow the intraoperative assessment of retinal traction.[20]

We have evaluated the role of liquid silicone or extended sulphur hexafluoride gas tamponade in combination with vitreous surgery and pneumatic retinal reattachment in the management of proliferative vitreoretinopathy. From this experience we have attempted to draw conclusions on the surgical management of PVR.

One of the most important surgical steps was the ability to assess relief of retinal traction intraoperatively. In 16 eyes intraoperative pneumatic retinal reattachment, by draining subretinal fluid through a pre-existing break or through an iatrogenic retinotomy while infusing air with an automated pump, allowed this crucial determination. In three eyes with previous vitrectomy surgery, preoperative fluid-gas exchange indicated the location and extent of the additional membrane dissection that was required to achieve adequate retinal reattachment. If we consider only those eyes in which we could achieve adequate retinal reattachment intraoperatively, we achieved long term anatomical success in 13 (76%) of 17 eyes.

The instillation of liquid silicone and assessment of retinal traction has been modified by different authors. Scott[9] combined external drainage of subretinal fluid with the instillation of intraocular silicone. He used indirect ophthalmoscopy to monitor residual retinal traction and subretinal silicone migration. Zivojnovic *et al.*[13] and Gonvers[14] have used silicone-fluid exchange under microscopic control combined with internal drainage of intraocular and subretinal fluid to assess retinal traction.

Techniques for fluid-gas exchange at the time of vitrectomy or prior to vitrectomy have also undergone modification. Charles[20] described hydraulic retinal reattachment for proliferative vitreoretinopathy. The use of an automated air infusion pump[21] to maintain a constant intraocular pressure, combined with improved visualisation in the air-filled eye using sodium hyaluronate on the corneal endothelium[22] and a biconcave lens[23] in the phakic air-filled eye, have enhanced pneumatic retinal reattachment techniques. Fluid-gas exchange techniques in eyes that have previously undergone vitrectomy surgery[24] have further enhanced preoperative and postoperative pneumatic retinal reattachment.

We used two different techniques for the instillation of silicone in the present study. In five eyes we performed a silicone-fluid exchange. In the remaining eight eyes we first attached the retina with air before filling the eye with silicone. The advantage of a fluid-silicone exchange is the ability to dissect epiretinal membranes when the retina is stretched by the silicone bubble. The major disadvantage is the tendency for silicone to migrate into the subretinal space if retinal traction is unrelieved and the difficulty both in visualising and treating this complication. Intraoperative pneumatic retinal reattachment using an automated air infusion pump to maintain a constant intraocular pressure, and the use of sodium hyaluronate applied to the corneal endothelium to achieve a clear view of the fundus, allow a variety of intraocular manipulations, including membrane dissection, retinotomy, and endolaser photocoagulation. Although subretinal migration of air and enlargement of retinal breaks are complications of this procedure, they are readily treated. In no case in this series did we infuse silicone into the subretinal space after successful pneumatic retinal reattachment. We were therefore able to avoid a major complication associated with silicone injection.[10]

The role of a broad scleral buckle in the treatment of PVR has been emphasised recently.[15 25 26] We found a broad buckle helpful in treating residual anterior loop contraction following vitrectomy and membrane dissection. A broad buckle was also helpful for recurrent detachment where it was possible to isolate anterior loop contraction and residual retinal detachment, with barrier photocoagulation on the scleral buckle after fluid-gas exchange.

The role of intraoperative laser endophotocoagulation in the treatment of retinal detachment and proliferative vitreoretinopathy has been emphasised.[15] This form of treatment was extremely helpful in those cases where the scleral buckle was not revised as well as for large retinotomies and posterior retinal breaks, both in the air filled and silicone filled eye. Intraoperative or postoperative photocoagulation of the retina overlying the scleral buckle 360° appears to be justified in view of the success we had in treating recurrent retinal detachments due to anterior loop contraction in silicone filled eyes and gas filled eyes.

The corneal complications noted in our aphakic patients treated with silicone have been described by other authors[10] and are presumably due to blocking aqueous nutrition of the corneal endothelium.[27]

Evaluation of retinal toxicity from silicone requires further detailed studies. In this study the best vision (20/100) resulted in a patient with intraocular silicone maintained for a six-month period. Recent electroretinographic (ERG) studies in patients with giant retinal tears treated with intraocular silicone versus sulphur hexafluoride gas appear to demonstrate the lack of short term retinal toxicity from silicone.[28] We have not noted unexplained visual deterioration in five patients with intraocular silicone ranging from seven months to 17 months, average 13 months.

If useful vision is defined as 5/200 vision or greater visual acuity, only four eyes out of 13 eyes that remain reattached achieved this level of acuity. In certain cases the macular distortion caused by epiretinal and subretinal membranes was an obvious, though not exclusive, source of the decreased vision. In other cases the macula appeared normal and we suspect a variety of other factors, such a poor photoreceptor regeneration following recurrent retinal detachments, as the source of the poor vision.[29]

It is difficult to compare the anatomical reattachment rates in those eyes treated with silicone versus those eyes treated with gas for several reasons. First, silicone oil was removed electively in only two of 13 patients. A more valid comparison would require removal of silicone oil in all eyes to approximate the gradual loss of intraocular tamponade by reabsorption of intraocular gas. Secondly, we switched to a gas tamponade in three eyes in which the retina became detached under silicone oil. Lastly, silicone oil was used in two eyes in which intraoperative pneumatic retinal reattachment was unsuccessful, whereas sulphur hexafluoride was used only after successful pneumatic retinal reattachment. Gonvers[14] reported a 62% anatomical success rate persisting after removal of silicone oil in eyes with PVR treated with vitrectomy and silicone oil. However, he did not reoperate on any eyes with recurrent retinal detachment under the silicone tamponade, a procedure which might have increased his anatomical success rate. Zivojnovic *et al.*[13] reported a 57% long term (two to four years) anatomical success rate using liquid silicone in combination with vitrectomy. Silicone was removed in 10% of cases and reoperation was performed with reinjection of silicone in 31% of cases. Removal of silicone resulted in redetachment in one-third of the cases.

In the present study seven (78%) of nine eyes were successfully treated with extended gas tamponade. Chang and coauthors have recently reported a 56% anatomical success rate for PVR using perfluoropropane to provide an extended gas tamponade following vitreous surgery.[30] An advantage of perfluoropropane over sulphur hexafluoride is the reduced number of postoperative gas-fluid exchanges necessary to maintain an effective tamponade. In the present study it was necessary to perform an average of three fluid gas exchanges in the postoperative period to maintain a gas bubble of 50% or greater of the intraocular volume for a three-week period. We injected additional aliquots of sulphur hexafluoride postoperatively that ranged from 20% to 60% without significant increases of intraocular pressure. We did not, however, perform total fluid gas exchanges, since the patients were seated at the slit-lamp and inferior intraocular fluid was never totally drained. This allowed room for expansion of the gas bubble when the concentration of sulphur hexafluoride exceeded 20%.

In three cases treated with gas tamponade that developed recurrent retinal detachment outpatient fluid-gas exchange accompanied by focal laser to the retinal break or widespread laser to the scleral buckle was sufficient to reattach the retina. In appropriate post-vitrectomy patients fluid-gas exchange accompanied by laser therapy, even when the retinal break cannot be visualised, may provide an effective means of reattaching the retina. If this procedure is successful, it eliminates the need for general anaesthesia and further intraocular surgery or scleral buckling.

De Bustros and Michels have stressed the biological time course of the proliferative process in PVR and suggested delaying intraocular surgery for six or more weeks.[26] We performed intraocular surgery after an average interval of 2·9 months (range one to seven months) from previous operations. This allowed time for the epiretinal membranes to become thicker and easier to grasp as well as allowing the proliferative and contractile process to stabilise. Nevertheless, reproliferation continues to be a problem.

Recurrent PVR occurred in 12 (71%) of 17 reattached retinas and was associated with eight of the 11 recurrent retinal detachments. The high percentage of eyes with recurrent PVR following vitrectomy has been emphasised by Machemer and Zivojnovic *et al.* Machemer,[19] using vitrectomy and gas tamponade, reported an initial reattachment rate of 68% to 47 eyes operated on for PVR, which decreased to 36% reattachment rate after six months. Zivojnovic *et al.*,[13] using vitrectomy and silicone tamponade, reported a three-month reattachment rate of 66% in 100 eyes, which subsequently decreased to 57% reattachment after a two- to four-year follow-up. The continued proliferation and contraction of intraocular cells emphasises the need for pharmacological treatment in these cases.[31]

Pneumatic retinal reattachment techniques have improved to allow intraocular surgical manipulations that previously were possible only in silicone filled eyes. Liquid silicone does not appear to be a highly effective tamponade for inferior retinal breaks and may cause ocular complications if not removed. Nevertheless, in patients who cannot tolerate the head positioning associated with gas tamponade, and in cases where retinal traction cannot be entirely relieved, silicone appears to be a useful intraocular tamponade. This description of surgical experiences emphasises the need for a prospective, randomised clinical trial to compare these two methods of tamponade. Such a study is under way.

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Estimation of visual function after optic neuritis: a comparison of clinical tests

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SUMMARY A group of 53 patients who had suffered an attack of unilateral (n=45) or bilateral (n=8) optic neuritis more than six months before were subjected to a battery of tests to determine their spatial contrast sensitivity, visual field, and colour vision. The 106 eyes investigated were classified according to their clinical status and visual acuity at the time of the study into unaffected (n=45), recovered (n=33), and non-recovered (n=28). At least one of the three tests gave an abnormal result in 67%, 88%, 100% of the three groups respectively. The results obtained with these three tests showed a significant statistical association.

Patients with optic neuritis (ON) generally have a good short-term prognosis as regards visual acuity as tested by Snellen types.[1 2] Normal vision is recovered in 50 to 78% of the patients within six months. However, in some cases ON produces long-lasting objective and/or subjective visual dysfunction.[3 4] There are strong indications not only clinically but also electrophysiologically that ON causes impairment of the optic nerve which may persist for a long time after the initial attack.[5-10]

Several authors claim that Snellen's test and similar tests of visual acuity measure only a limited aspect of visual perception,[11-13] since it has been found that the visibility of objects depends not only on their sizes at high contrast but also on their luminance relative to the background.

Optic neuritis and multiple sclerosis (MS) patients have been found to have abnormal contrast sensitivity in combination with normal visual acuity.[14-17] This suggests that the Snellen test of visual acuity may be an inadequate measure of visual function in investigations of the degree of recovery after ON.

In the present study clinical tests of visual function (including determination of spatial contrast sensitivity, colour vision, and visual field) were applied to a group of 53 persons, who had an attack of ON from six months to 3·5 years before the start of the study. The main aim was to determine which combination of these tests gives the best measure of visual function after ON, especially in those cases where the Snellen visual acuity is ≥1·0, suggesting (nearly) complete recovery of visual function. Since there is disagreement about the presumed higher risk of MS after bilateral optic nerve involvement,[3 18] we performed the above set of tests on both eyes of all test subjects, to see whether these tests offered a sensitive means of detecting asymptomatic optic nerve involvement.

Patients and methods

PATIENTS

Fifty-three patients (40 female, 13 male) treated for acute ON at the Eye Clinic of Erasmus University, Rotterdam, between 1980 and 1983 were re-examined at the same clinic in 1984 for the present study. The diagnosis of ON was mainly based on the presence of features as summarised by Glaser.[19] A pattern visual evoked response (PVER) was recorded in order to support the diagnosis electrophysiologically. The patient's age at the time of the study ranged from 17 to 54 years (mean 32 years).

Eleven patients had had a relapse of ON within the period from 1980 to 1984. In eight of them the recurrence affected the contralateral, initially unaffected eye, while in the other three cases the relapse was on the ipsilateral side. At the time of this investigation 29 of the 53 patients had clinical signs and symptoms of mild central nervous system (CNS) involvement affecting structures other than the optic

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Table 1 *Classification of eyes*

Classification		*Clinical signs and symptoms in this eye during ON attack*	*Snellen visual acuity during present study*
Unaffected	(n=45)	No	>1·0
Recovered	(n=33)	Yes	>1·0
Non-recovered	(n=28)	Yes	<1·0

nerve, which was regarded as justifying the diagnosis of clinically probable or possible MS as defined by the criteria of McAlpine *et al.*[20]

The eyes investigated were classified on the basis of clinical status and Snellen visual acuity as unaffected, recovered, and non-recovered on the basis of the criteria shown in Table 1.

METHODS

Contrast sensitivity was determined with equipment based on the modified Von Bekesy tracking method.[21] Vertical sinusoidal gratings presented on a television monitor at a mean luminance of 5 cd/m^2 were used as stimuli. The contrast sensitivity was determined in the spatial frequency range from 0·1 to 25·6 cycles per degree (c/deg). The stimulus was 8° wide for the range 0·8 to 25·6 c/deg and 32° wide for the range 0·1 to 0·4 c/deg to prevent the contrast sensitivity from being influenced by two small a number of cycles at low spatial frequencies.[22-24] To prevent afterimages the grating was counterphased every 0·8 s. Further details have been described previously.[25]

The abnormal range of contrast sensitivities was determined on the basis of measurements on both eyes of 26 controls—that is, persons without known subjective or objective ophthalmological complaints. The control group was age and sex matched with the ON group. A contrast sensitivity more than 2 standard deviations below the normal value in the low (0·1 to 0·4 c/deg), medium (0·8 to 3·2 c/deg), or high (6·4 to 25·6 c/deg) spatial frequency range was considered as abnormal.

Visual acuity was determined with a Snellen chart and expressed as the reciprocal of the mean angle of resolution in minutes of arc. A visual acuity of 1·0 or more was considered normal.

Colour vision was examined under standard conditions by the Hardy Rand Rittler (HRR) and desaturated panel D-15 tests. Normal values were obtained in 25 control subjects according to the code of Verriest.[26] The results of the HRR and panel D-15 tests showed a very strong statistical association ($p<0·001$). We therefore decided to pool the results of these two tests for the purposes of comparison with the other measures of visual function considered in this study.

Table 2 *Incidence of abnormal contrast sensitivity function in all eyes investigated*

Spatial frequency range	*Incidence of significantly reduced contrast sensitivity in:* *Unaffected eyes*		*Recovered eyes*		*Non-recovered eyes*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Low	2	4	2	6	0	0
Medium	0	0	0	0	1	4
High	6	13	3	9	2	7
Low+medium	0	0	1	3	1	4
Low+high	0	0	1	3	2	7
Medium+high	0	0	1	3	1	4
Low+medium+high	4	9	5	15	19	68
Total	12	27	13	39	26	93

Visual fields were determined with the 'computerised octopus display'.[27] Visual field defects were classified as either central or paracentral.

Clinical ophthalmological and neurological examinations were performed on all 53 patients. During these examinations the patients were asked whether they had only subjective visual complaints.

Statistical analysis was performed with the SPSS computer program. Differences between sets of experimental data were tested for significance by the Wilcoxon,χ^2, and Kendall's t-B and t-C or by regression analysis.

Results

CONTRAST SENSITIVITY

The mean contrast sensitivity curves for all three groups of eyes (unaffected, recovered, and non-recovered) were lower than normal, that for the non-recovered eyes being lowest (Fig. 1). The highest incidence of contrast sensitivity abnormalities (93%) was found in the impaired eyes, the corresponding figures for the recovered and unaffected eyes being much lower (39% and 27% respectively; Table 2). The abnormality most frequently found in the overall group of eyes with decreased contrast sensitivity (n=51) was a reduction in contrast sensitivity for all spatial frequency ranges investigated (n=28; Table 2).

VISUAL ACUITY AND CONTRAST SENSITIVITY

As may be seen from Fig. 2, a significant correlation was found between visual acuity and contrast sensitivity in each of the three frequency ranges employed, the correlation coefficients for the high, medium, and low ranges being 0·59, 0·65, and 0·71 respectively. A significant correlation ($r=0·68$) was also found between the visual acuity and the grating acuity (that is, the spatial frequency at which the

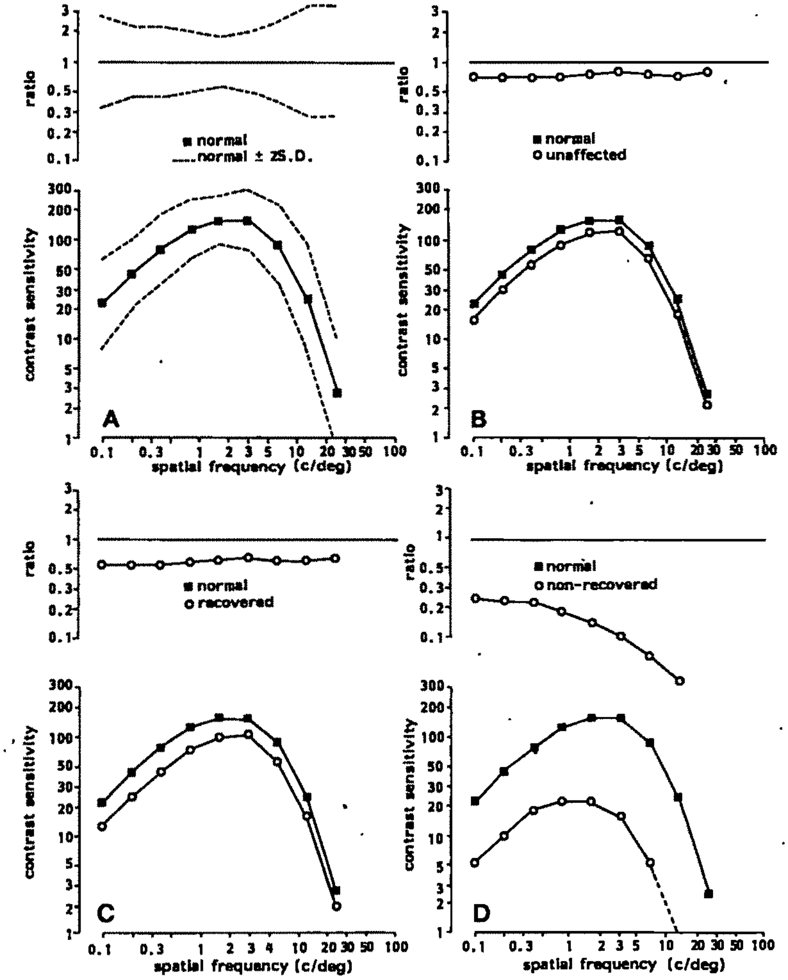

Fig. 1 *Contrast sensitivity as a function of spatial frequency for* (A) *normal eyes,* (B) *unaffected eyes,* (C) *recovered eyes, and* (D) *non-recovered eyes. The curve for normal eyes is repeated for the sake of comparison in each of Figs. 1B, C, and D, and the ratio of the contrast sensitivity for the group of eyes in question to that for normal eyes is plotted against the spatial frequency at the top of each graph. In Fig. 1A the broken lines represent the confidence limits (mean value±twice the standard deviation); the ratio of these limits to the mean value is also plotted at the top of this graph.*

extrapolated contrast sensitivity equals 1·0). This is also shown in Fig. 2.

COLOUR VISION AND VISUAL FIELD DEFECTS IN RELATION TO CONTRAST SENSITIVITY

Significant associations were found between reduced contrast sensitivity in the low, medium, and high spatial frequency ranges and defects of colour vision and visual field (Table 3). Moreover, central and paracentral visual field defects also showed an association with reduced contrast sensitivity when considered separately. This is probably due to the fact that these two types of visual field defects were likewise statistically associated ($p<0·001$). Furthermore, colour vision disorders showed a significant association with visual field defects ($p<0·001$).

ASYMPTOMATIC OPTIC NERVE INVOLVEMENT

Table 4 surveys the results of all clinical and paraclinical examinations of the unaffected, recovered, and non-recovered eyes. All non-recovered eyes ($n=28$) and 88% of the recovered eyes ($n=33$) had at least one defect. Even 30 (67%) of the eyes that had never been attacked by ON at a clinical level showed one or more visual abnormalities. This asymptomatic optic nerve involvement could perhaps be explained by demyelination in the contralateral optic nerve. In other words there is reason to believe that many of our patients were actually suffering from bilateral optic nerve involvement.

Since bilateral ON is thought to be associated with a high risk of subsequent development of MS,[3] it is instructive to see how many of our patients did actually have signs and symptoms of MS at the time of the present study. In fact 29 of our 53 patients showed signs and symptoms of mild CNS involvement affecting structures other than the optic nerve (limb paraesthesiae 38%, limb paresis 18%, diplopia 12%, cerebellar ataxia 9%, bladder dysfunction 9%, Lhermitte's sign 6%, facial paresis 3%). Asymptomatic optic nerve involvement tended to be found more often in the patients who had signs and symptoms of MS (18 out of 29). However, this tendency is not statistically significant (χ^2 test yielded $p>0\cdot05$ for all combinations; not shown in the tables).

SUBJECTIVE VISUAL SYMPTOMS AND CONTRAST SENSITIVITY

Subjective complaints were mentioned by 38 patients and attributed to 42 out of 106 eyes. They were of blurred or misty vision in 32, colours which seemed paler than normal in 20, and silhouette vision in 11. Contrast sensitivity was decreased in 30 of these 42

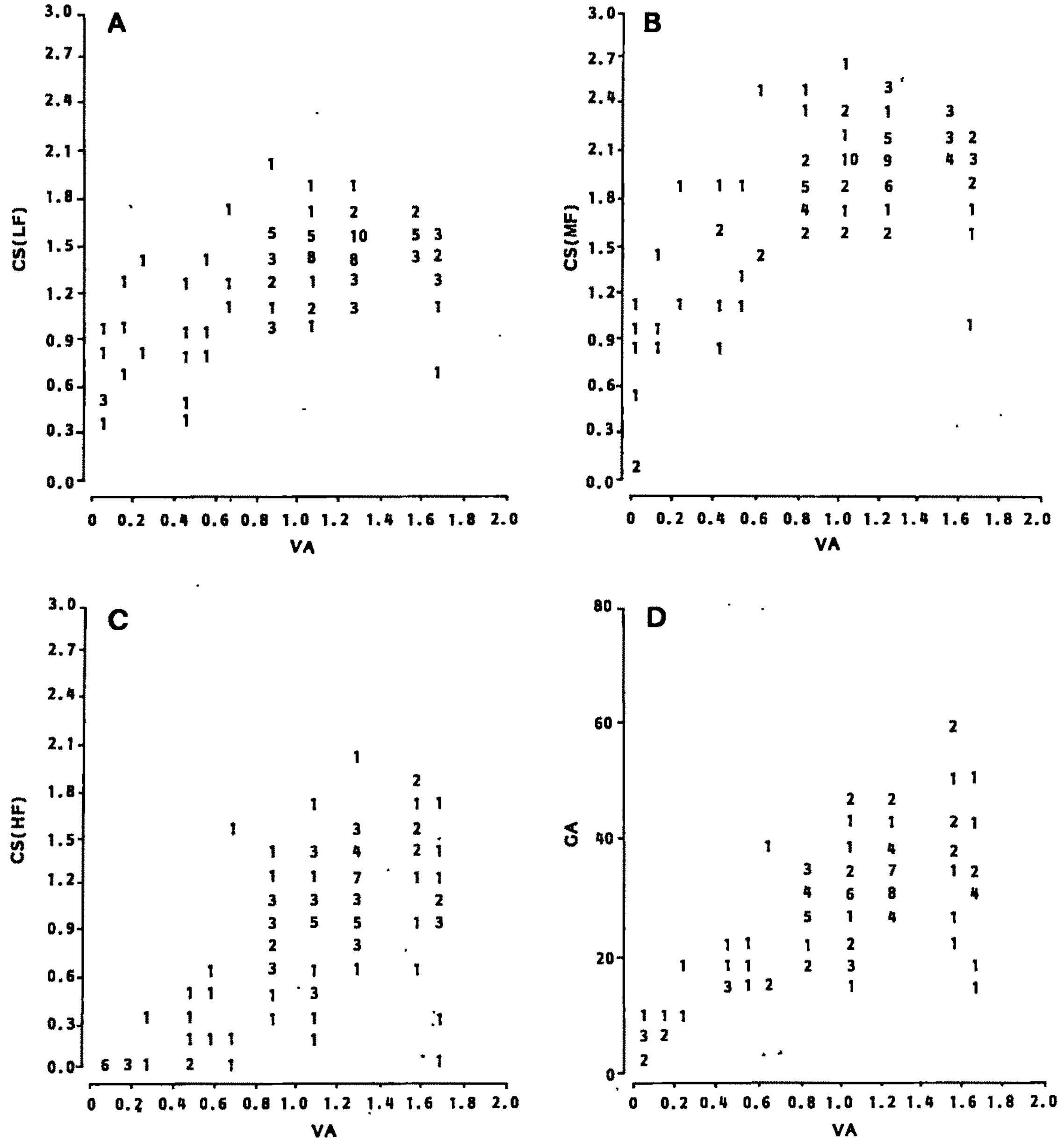

Fig. 2 *Scatter diagrams showing correlation of visual acuity with contrast sensitivity for* (A) *low spatial frequencies (0·1–0·4 c/deg),* (B) *medium spatial frequencies (0·8–3·2 c/deg), and* (C) *high spatial frequencies (6·4–25·6 c/deg).* D: *correlation of visual acuity with the 'grating acuity'—that is, the spatial frequency at which the extrapolated contrast sensitivity equals 1·0.*

Table 3 *Association between the various visual tests and abnormal contrast sensitivity*

Number of eyes with			*Incidence (%) of significantly reduced contrast sensitivity, in the*		
			Low	*Medium*	*High*
			spatial frequency range		
Defective colour vision:	Yes	33	61	61	64
	No	73	23	18	32*
Reduced visual field:	Yes	31	65	65	71
	No	71	21	13	28
Subjective symptoms:	Yes	42	55	60	64
	No	64	22*	13	27

*In these cases the association between reduced contrast sensitivity and the clinical symptom in question is significant at the p<0·01 level; in all other cases shown in this table this association is significant at the p<0·001 level.

(71%). The other tests yielded lower percentages of abnormalities in the eyes associated with subjective complaints: colour vision was affected in 62% and the visual field in 56%. Diminished contrast sensitivity and defects of colour vision and of the visual field showed a statistically significant association with subjective complaints (p<0·001; not shown in the tables).

COMBINATION OF TESTS

As may be seen from Table 5, more defects of visual function can be detected if two or more tests were combined. In the non-recovered group 19 of the 27 eyes (70%) gave abnormal results in all three tests, while all eyes in this group gave abnormal results in one or more of the three tests. At the other extreme, in the 'unaffected' group none of the eyes gave abnormal results in all three tests, and only 19 out of 44 (43%) showed signs of a visual defect in at least one test.

Table 4 *Incidence of abnormal visual tests in unaffected, recovered, and non-recovered eyes*

Function tested	*Incidence of abnormalities found in:*		
	Unaffected eyes (n=45), %	*Recovered eyes (n=33), %*	*Non-recovered eyes (n=28), %*
Clinical			
Pallor of disc	9	76	93
Visual field			
Central scotoma	4	15	33
Paracentral scotoma	2	12	71
Colour vision			
HRR	7	18	71
Panel D-15	13	12	68
Subjective complaints			
Fogginess	7	30	68
Pale colours	0	15	54
Other	0	0	29
Reduced contrast sensitivity	27	39	93
Total*	67	88	100

*This total is not equal to the sum of the figures given above, as many eyes showed more than one abnormality.

Discussion

INCIDENCE OF TEST ABNORMALITIES IN THE THREE GROUPS OF EYES

The first question we set out to answer was whether these tests, alone or in combination, provide us with more information than Snellen's test of visual acuity. The short answer is Yes. As may be seen from Table 5, 100% of the non-recovered eyes (visual acuity <1·0) showed abnormalities in one or more of the three tests. Our data for these non-recovered eyes are comparable with published findings on ON in the acute stage: disturbed contrast sensitivity in 63 of 100%,[15 28] visual field defects in 61 to 92%,[29] colour vision defects in 63 to 99%.[30 31]

The overall incidence of test abnormalities (55%) in the recovered eyes (visual acuity >1·0) is naturally lower than in the non-recovered eyes. The only comparable findings in the literature are those of Kirkham and Coupland,[32] who found 53% colour vision abnormalities in 93 patients. However, these authors gave no information about visual acuity in

Table 5 *Cumulative incidence of the combination of test abnormalities in unaffected, recovered, and non-recovered eyes*

Function tested	*Incidence of abnormalities found in:* *Unaffected eyes, %*	*Recovered eyes, %*	*Non-recovered eyes, %*
Colour vision	14	19	74
Visual field	5	19	85
Contrast sensitivity	27	39	93
Colour vision *and* visual field	0	6	70
Colour vision *and* contrast sensitivity	2	10	74
Visual field *and* contrast sensitivity	—	10	78
Colour vision *and* visual field *and* contrast sensitivity	—	3	70
Colour vision *or* visual field	18	32	89
Colour vision *or* contrast sensitivity	39	48	93
Visual field *or* contrast sensitivity	32	48	100
Colour vision *or* visual field *or* contrast sensitivity	43	55	100

their patients and did not test the visual field or the contrast sensitivity. Some other authors[16 29 33 34] had also reported that suitable tests could detect visual defects in eyes that showed clinical recovery from ON; however, these studies concerned smaller numbers of patients.

A more surprising result was obtained in the clinically unaffected eyes in our study. No fewer than 19 of these 45 eyes (43%) showed at least one abnormal result in our three visual function tests (Table 5). The contrast sensitivity yielded the highest frequency of abnormalities in all groups and the highest association with subjective complaints.

ASYMPTOMATIC OPTIC NERVE INVOLVEMENT

The finding of 'subclinical' abnormalities in 43% of the 'unaffected' eyes leads us to a second question: is bilateral optic nerve involvement more indicative of MS than unilateral involvement? On the basis of the evidence gathered during the present study the answer to this question must be No. Five of the eight patients who had suffered clinical attacks on both eyes (see under 'Patients' above) belonged to the group of 29 patients with mild CNS involvement, while the other three patients with bilateral attacks showed other signs, attributable to multiple CNS lesions. A similar picture was obtained in the 30 'unaffected' eyes showing one or more abnormalities in one of our three visual function tests or on clinical examination or associated with subjective complaints (Table 4); only 18 from this group were associated with any signs of other CNS structures. These data stress the evidence that bilateral optic nerve involvement, either simultaneous or sequential, does not include a higher risk of development of MS. These data only partly support the report of Parkin *et al.*,[18] who found a higher risk after bilateral simultaneous ON but not after bilateral sequential ON.

ASSOCIATIONS BETWEEN THE TESTS

Contrast sensitivity abnormalities were found in 39% of the recovered eyes in our study and in 27% of the unaffected eyes. This confirms earlier findings that normal visual acuity on Snellen testing (1·0 or more) need not always coincide with normal contrast sensitivity.[14–16] However, none of the previous authors subjected their results to statistical analysis in view of the relatively low numbers of patients involved. As shown in Fig. 2, we found a statistically significant correlation between visual acuity and contrast sensitivity in all three spatial frequency ranges. This finding seems at first sight paradoxical in view of our observation, mentioned above, that an appreciable proportion of persons with normal visual acuity (>1·0) nevertheless show a marked drop in contrast sensitivity.

However, the following consideration may help to reconcile these two sets of observations. The results shown in Fig. 2 seem to establish that there is a general tendency for a higher visual acuity to be associated with a higher contrast sensitivity. But there is a very appreciable variation about this trend, so that if we consider only good eyes, or consider only bad ones, the trend is not persistent in relation to all eyes investigated and results plotted in one curve (Fig. 2). It is only when we consider a population with a sufficiently wide range of visual function that the statistical significance of the trend becomes clear. It now becomes understandable that, in view of the above mentioned spread in the results, many eyes may have a significantly low contrast sensitivity.

The presence of the spread in the correlation curves of Fig. 2 allows a further conclusion to be drawn, namely, that persons with a given visual acuity as measured by the Snellen chart may have an appreciably worse (or appreciably better) contrast sensitivity than might be expected. This would seem to indicate that visual skills other than the perception of contrast play an appreciable part in the correct perception of the letters on the Snellen chart.

This conclusion is in line with the claim by Campbell[11 12] and Wollner and Diamond,[13] mentioned above; Snellen's test and similar tests of visual acuity measure only a limited aspect of visual perception.

The significant association we observed between reduced contrast sensitivity and defective colour vision and visual field (Table 3) is hard to understand, since each of these various types of defect may be expected to arise by a different physiological mechanism. The common factor in all these cases might possibly be a demyelinative attack on the optic nerve during the ON episodes.

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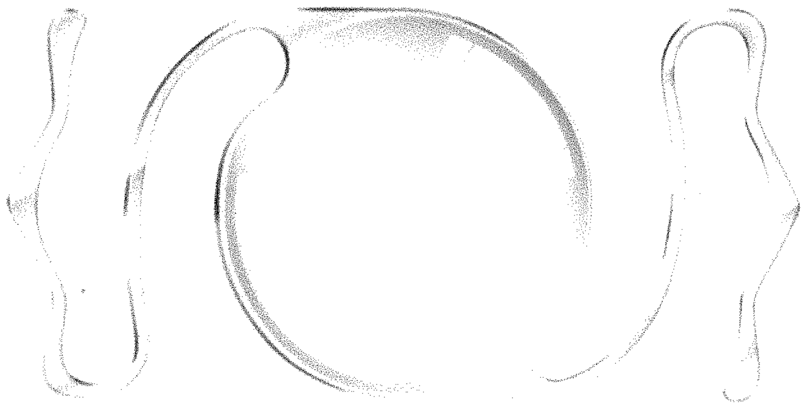

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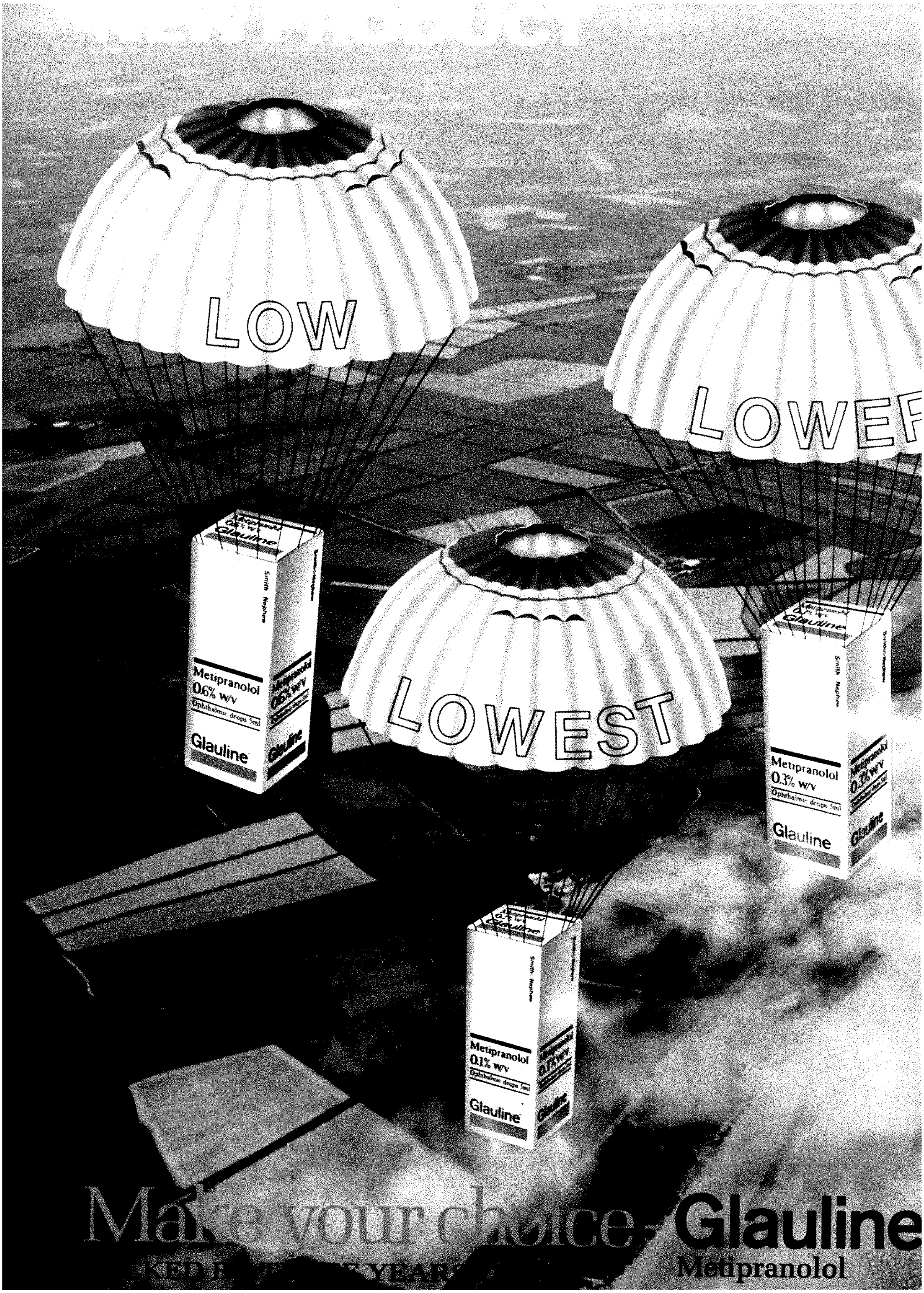
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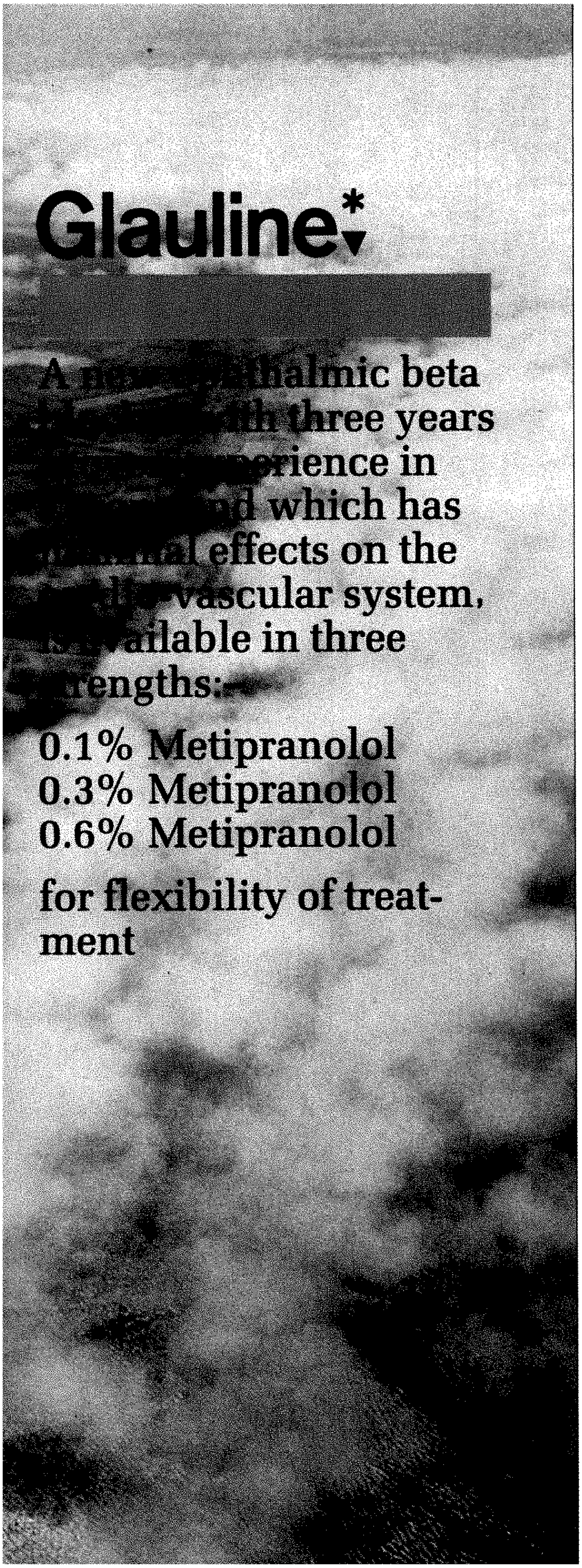

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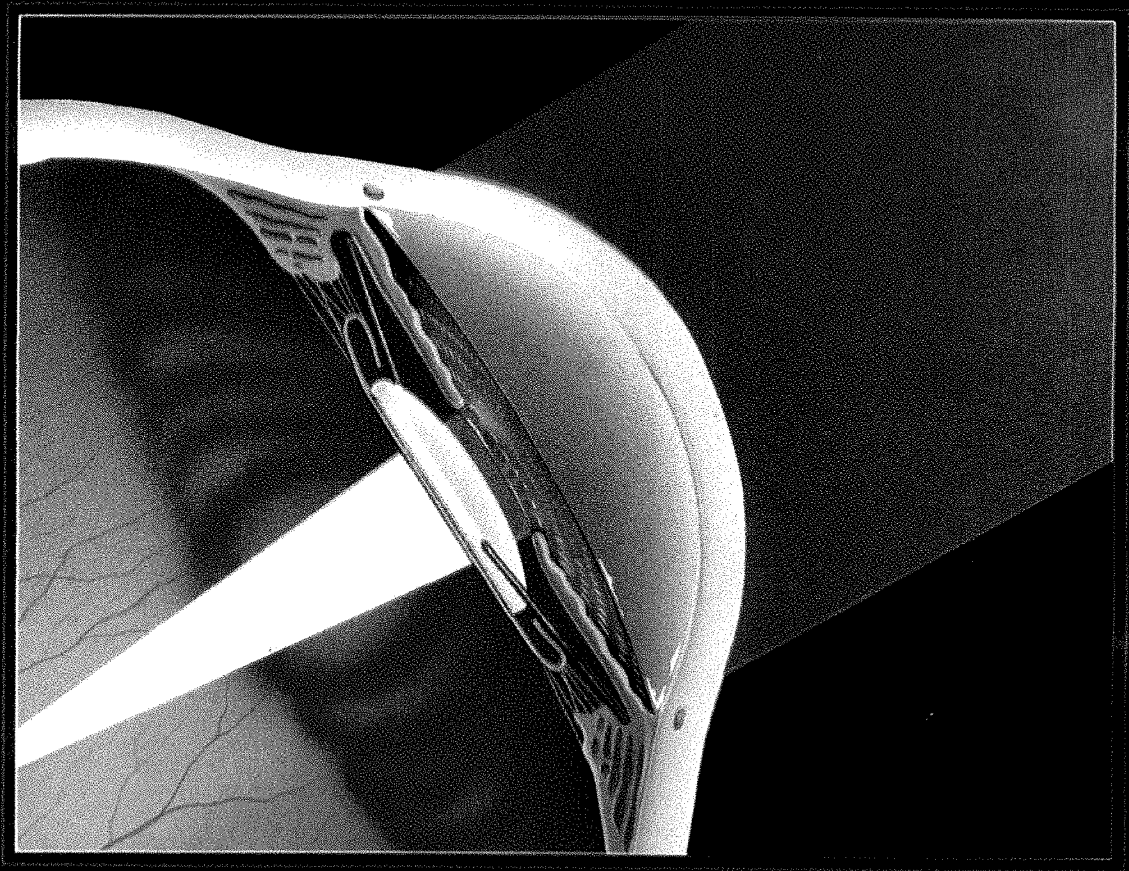

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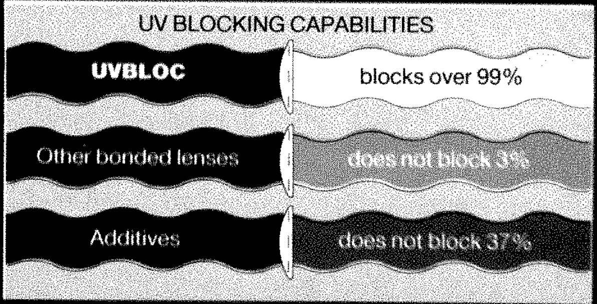

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British Journal of Ophthalmology, 1986, **70**, 925–930

New method for visualising discontinuities in the crystalline lens

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SUMMARY When the illuminating beam of a slit-lamp is polarised and one of the viewing oculars and the camera lens are provided with crossed analysers, the image of the lens generally darkens. The effect is enhanced by the insertion of a quarter-wave plate. The contrast of lenticular discontinuities is consequently greatly accentuated. This makes it possible to quantify them.

The conventional description of a slit-lamp image is said to pick out the cornea, the 'optically' empty space of the aqueous, and the white mass of the lens. The bluish colour is attributed to light being scattered by the lens, increasingly so as age advances. Sometimes reference is made to the third and fourth Purkinje images, with the latter appearing comparatively yellow because short-wavelength radiations are preferentially scattered and/or absorbed as they traverse the lens, so leaving the complementary tint in the posterior reflexion. This picture is accentuated when a cataract is present.

However, this account harbours some unexplained observations. It is a matter of common clinical experience that the patient's vision is often subjectively far better than an objective appraisal of his lens would lead one to believe. Furthermore, Zuckerman *et al.*,[1] who studied the image-forming attributes of excised lenses with artificially produced 'cataracts', also emphasised the advanced stage of deterioration needed for the production of optically adverse consequences to be realised.

These difficulties would be resolved if it were to turn out that what appears to be light scatter may not conform to the conventional definition which entails the notion of randomness. It is well known that scattering media tend to depolarise radiation that is initially polarised, and this provides consequently a test for the optical nature of doubtful media.[2] It is of course important to allow for the angle between the incident and the scattered light: the latter may contain a significant moiety of polarised light at 90°.

Although polarised light has been used for the study of the human eye in the past,[3] the procedure does not appear to have been used clinically. It has recently been found that if, in addition to being provided with a pair of crossed polaroids, a slit-lamp beam passes through a suitable quarter-wave plate which compensates for the birefringence of the cornea and is rotatable, the well-known Maltese cross[4] can be made to move across the pupil. Consequently, any part of the lens can be occluded in a manner that is quantifiable.[5] One would expect occlusion to be less effective in the presence of scattering nuclei, and the fraction of real to apparent scatter indeed rises with age.

However, it is only in the eighth or ninth decade of life that the distinction between the two tends to vanish. What, then, happens if a cataract is present? Conversely, is it possible that the apparent scatter impedes the detection of optical discontinuities in the lens and that, if such scatter were reduced, we would see a more informative picture not otherwise available for diagnosis? It may be mentioned parenthetically that Peli[6] has recently used a non-crossing polarised-retarded system to enhance contrast in the corneal endothelium.

Material and methods

A Zeiss photographic slit-lamp was modified in the following manner. A piece of polaroid (axis horizontal) was placed over the illuminating beam, and one piece (axis vertical) each over the camera beam and the left ocular. In addition a rotatable quarter-wave plate (λ=529 nm) was placed between the first piece of polaroid and the patient's eye. Although polaroid with a transmission factor T=22% would have been desirable, the output of the flash tube

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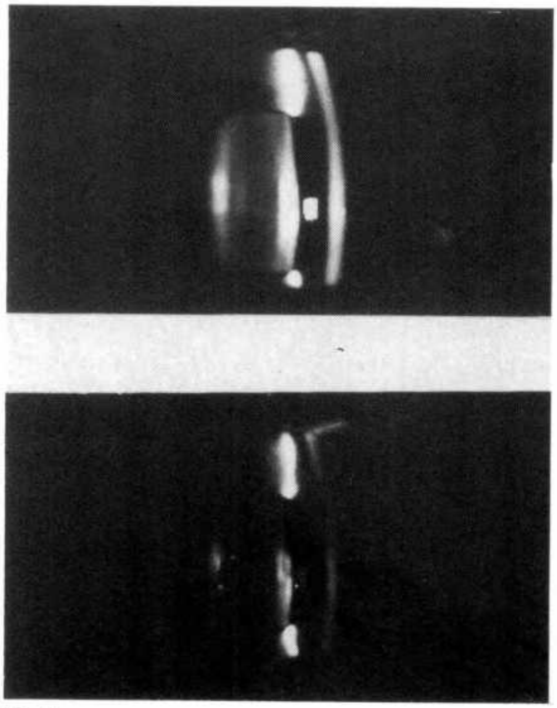

Fig. 1

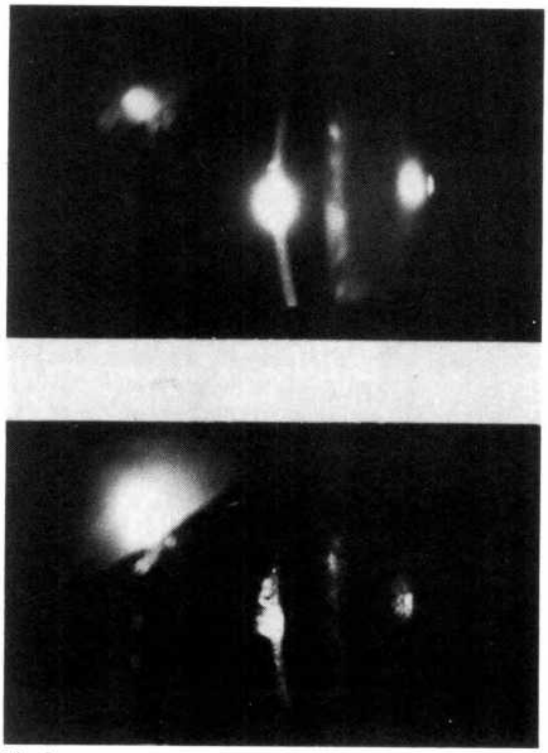

Fig. 2

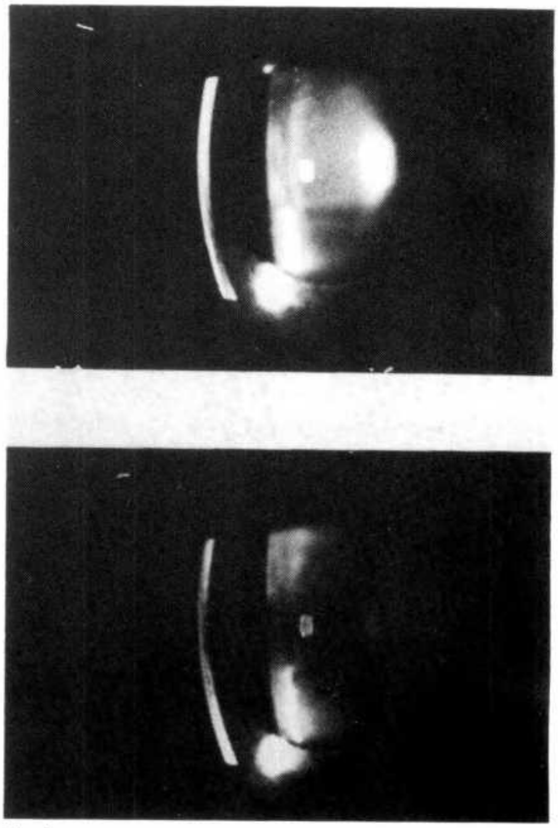

Fig. 3

made photography difficult, and therefore a transmissivity of T=43% had to be tolerated. For clinical visual use the better type is preferable, as it enhances contrast.

For the purpose of a photographic demonstration the quarter-wave plate was rotated so as to minimise and maximise contrast in selected parts of the field. In the former case the picture approached that seen in conventional viewing, as is to be expected on theoretical grounds.[7]

Results

Typical comparisons as between the conventional and the more novel appearances are shown in the following illustrations. In general the conventional view is placed at the top.

Fig. 1 shows the appearance for a normal 48-year-old lens. The normal scatter in the lens and cornea is diminished in the lower picture. The lens is optically evacuated, and water-clefts, not normally visible, appear in the anterior part of the lens.

Fig. 2 shows, for another eye, not only that the

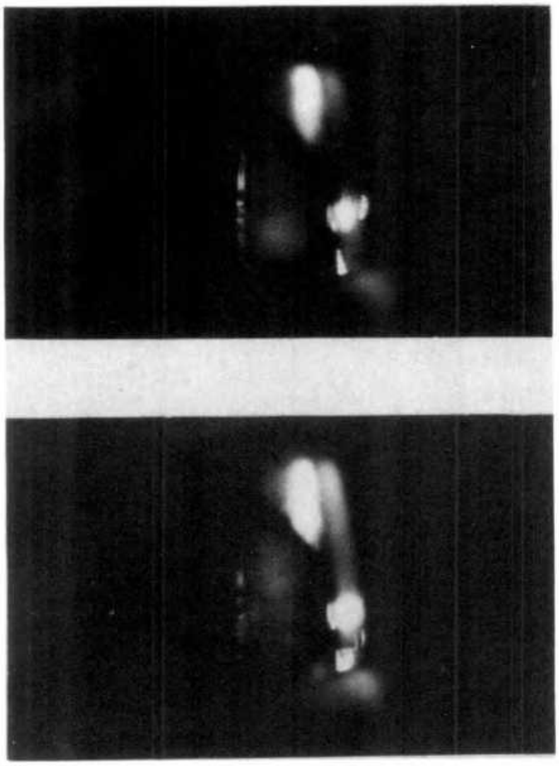

Fig. 4

clefts can be effectively isolated, but also that when the slit-lamp is focused on the cornea the corneal criss-cross drawn and explained by Koeppe[2] is superposed on the image.

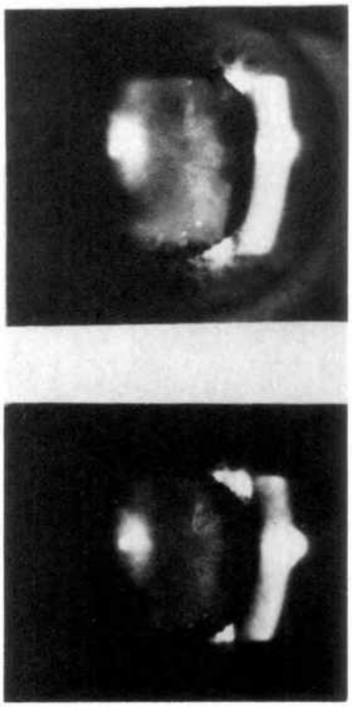

Fig. 6

Fig. 3 provides evidence in support of the view that the optical 'evacuation' of the lens fails in places of pronounced scattering agglomerates, as indicated in the lower part of the lens.

Fig. 4 illustrates not only a posterior subcapsular cataract but also shows that a nuclear cataract is

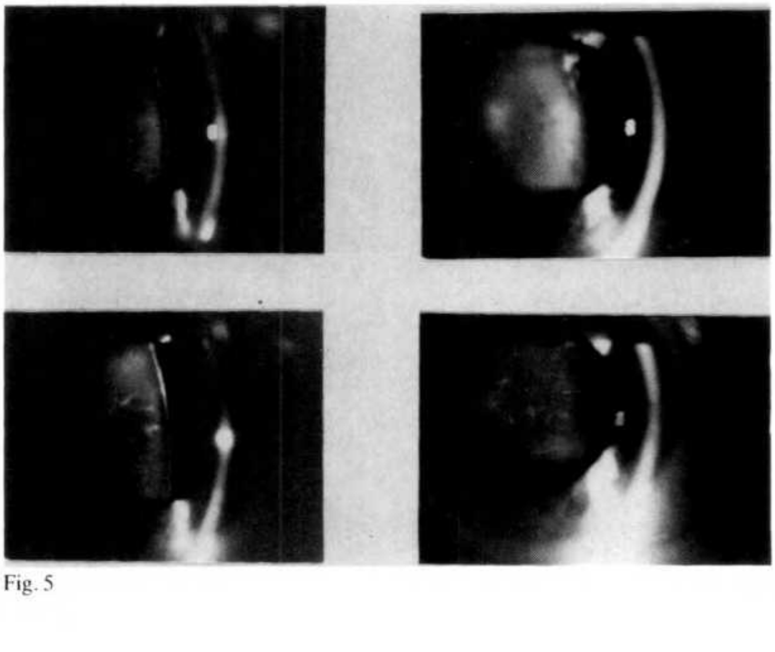

Fig. 5

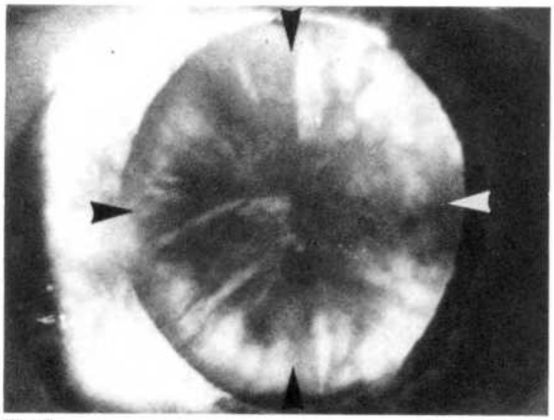

Fig. 7

present. However, rotation of the quarter-wave plate (Q) enables one to darken different parts of the lens thereby revealing water clefts (cf. lower picture). This illustration also shows that a nuclear cataract does not contain only randomly scattering discontinuities: if it did, then the rotation of Q should be without effect on the distribution of the light in the nucleus.

Fig. 5 shows a dense nuclear (brunescent) cataract. The two bottom pictures indicate the presence of clearly visible discontinuities, made manifest by the

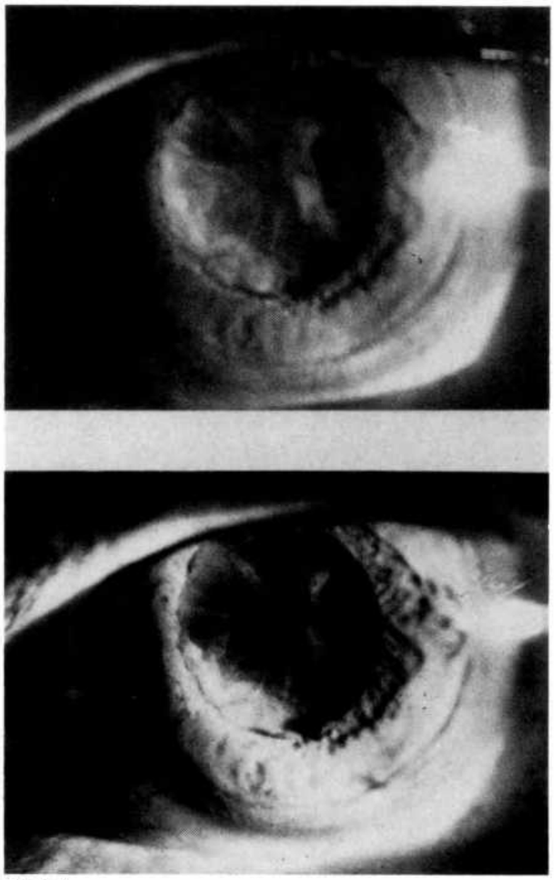

Fig. 8A

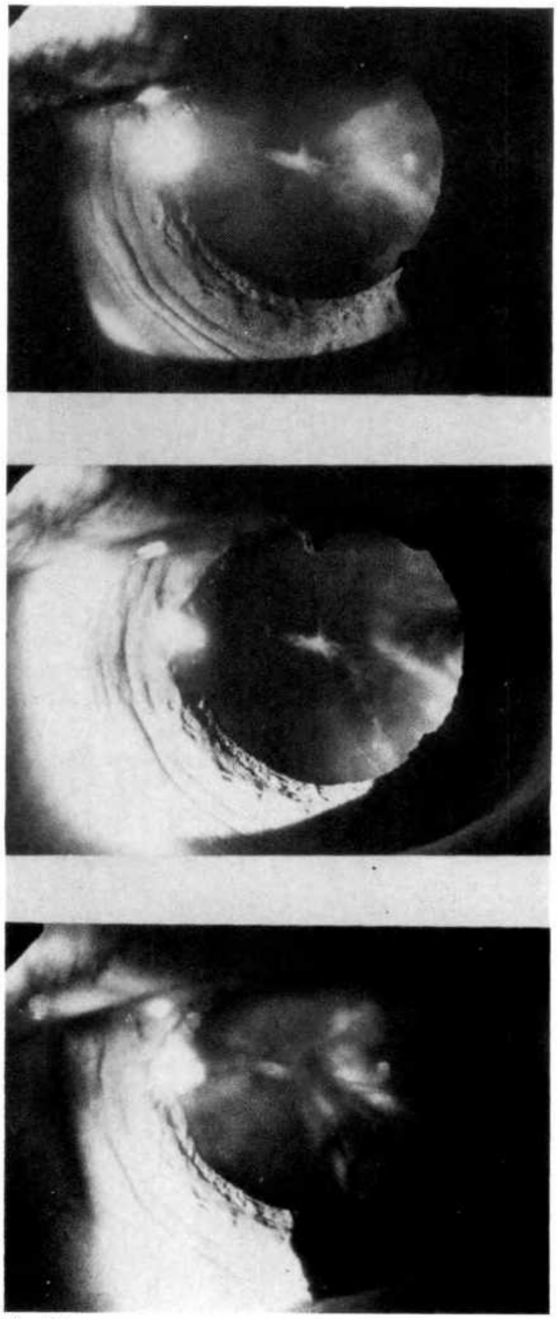

Fig. 8B

appropriate angular position of the Q plate. Note their appearance in the side and frontal views respectively.

Fig. 6 highlights the increase in contrast obtainable in a case of generalised scatter and cuneiform cataract, which may be of value in monitoring progress in either direction.

Fig. 7 also illustrates the extent to which the presence of the 'Maltese cross' (arrows) may make measurement of discontinuties a realistic proposition.

Figs. 8A, B. These sequences refer to the left and right eyes of one patient. Fig. 8A demonstrates the increase in contrast and, in addition to doing this, Fig. 8B shows that detail, including albumin deposits, can be revealed at different depths in the lens.

An example of a coronal cataract is shown in Fig. 9. Note how the reflexion from the posterior surface of the lens is virtually eliminated. Owing to the birefringence of the ocular media, the positions of Q for minimising the intensities of the two principal reflexions are slightly dissimilar.

In Fig. 10 there are to be seen pepper-pot signs and

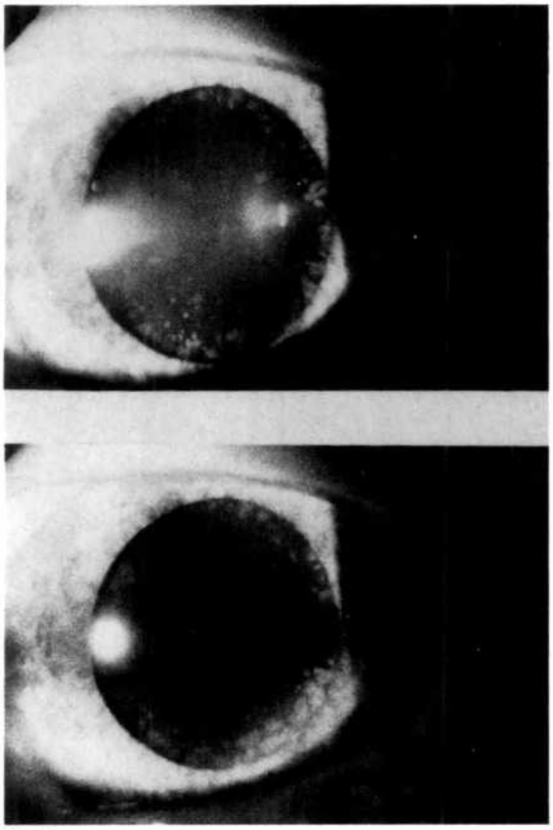

Fig. 9

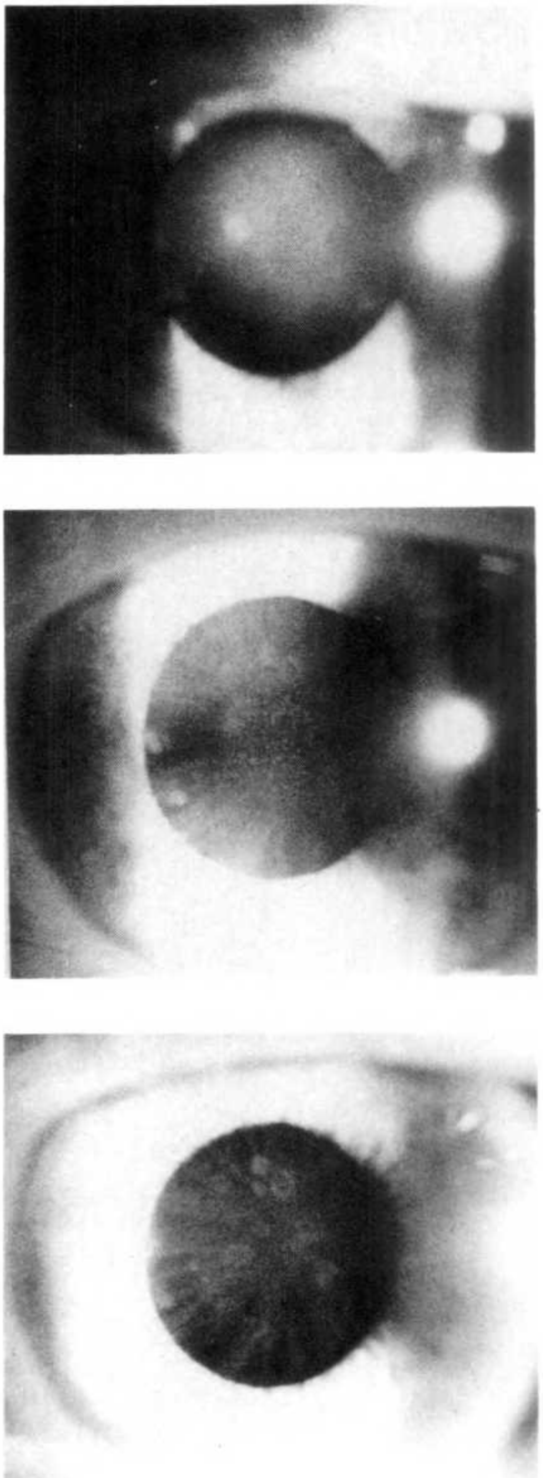

Fig. 10

striae of diabetes (cf. Fisher[8]) and also calcium deposits, which are largely invisible in the conventional top picture.

Discussion

Several of the above illustrations support the suggestion deduced from observations on normal lenses[4] that one has to distinguish apparent from real lenticular light scatter. The former can, but the latter cannot, be modified by the use of polarised light. The degree of modification is less marked in cases of nuclear cataract, but is rarely negligible. It would seem to follow that the use of the optical modifications described above is useful for the following reasons: first, one is enabled to see structural changes that remain obscured by scatter in normal viewing; secondly, such changes may facilitate a differential diagnosis; thirdly, the technique makes it possible to quantify lenticular discontinuities and to monitor their changes, if any.

I thank Professor R F Fisher for the loan of a Zeiss photo slit-lamp and helpful discussions, and Miss G M Villermet for technical assistance.

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Primary epitarsus: a case report

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SUMMARY Epitarsus is a rare congenital anomaly or may be acquired following severe conjunctivitis, usually of a cicatrising nature. The terms primary and secondary epitarsus are suggested to denote the two different aetiological varieties. On its clinical and histopathological features the present case conforms to the interfornix variety of primary epitarsus.

Epitarsus is a peculiar condition which typically occurs as an apron-like fold of conjunctiva attached to the inner surface of the upper lid but occasionally as a bridge of tissue under which a probe may be passed.[1] It is known to occur as an end result of neglected conjunctivitis, particularly purulent, pseudomembranous, and trachomatous,[2,3] and also as a congenital anomaly without signs of inflammation.[1]

Epitarsus occurring as a congenital anomaly is rare, and still rarer is the interfornix variety found in the present case, which therefore seems worth reporting.

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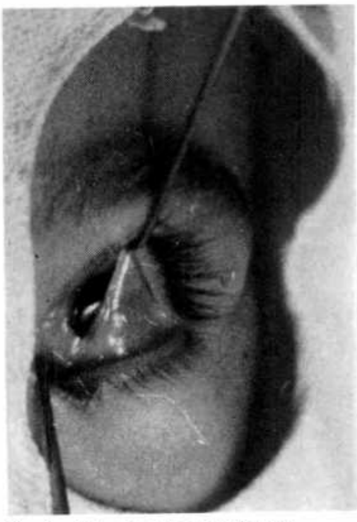

Fig. 1 *Showing the membrane extending from upper fornix to lower fornix (interfornix epitarsus).*

Case report

This 3-month-old male child had a history of membrane in the left eye since birth. There was no history of redness, discharge, or ocular trauma (mechanical, chemical, or thermal). Delivery of the child had been normal. Systemic examination did not reveal any abnormality. The family history had nothing of relevance to the case.

Ocular examination showed a conjunctival fold extending vertically from the upper to the lower fornix over the temporal aspect of the left globe, including part of cornea (Fig. 1). The fold was pinkish white, unassociated with any other anomalies, and was not adherent to the underlying eye ball. The medial border of the fold was free, and a probe could be passed under it easily. Extraocular motility was normal, and there was no blepharoptosis. Fig. 2 shows the appearance after surgical excision of the membrane. The right eye was normal.

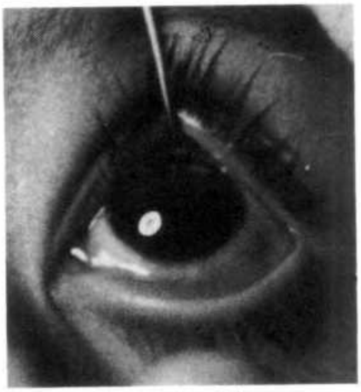

Fig. 2 *After excision of the membrane.*

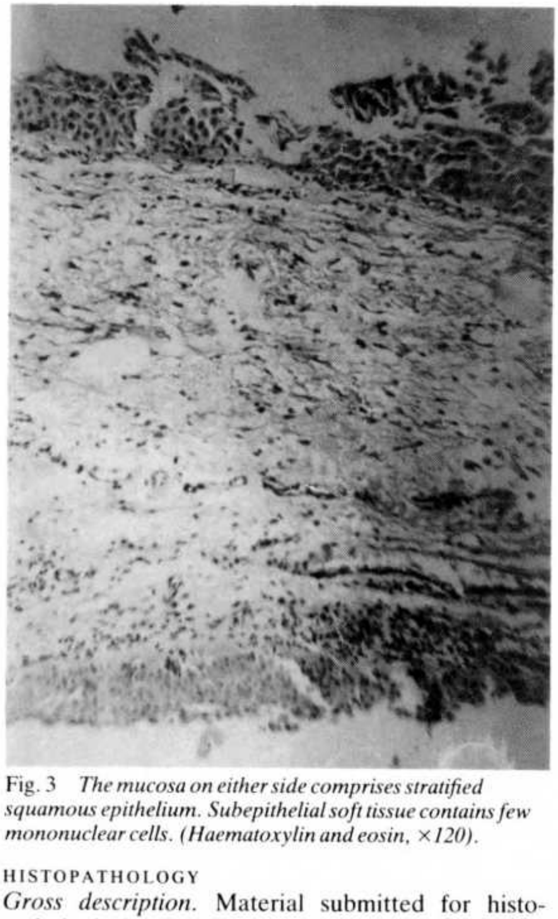

Fig. 3 *The mucosa on either side comprises stratified squamous epithelium. Subepithelial soft tissue contains few mononuclear cells. (Haematoxylin and eosin, ×120).*

HISTOPATHOLOGY

Gross description. Material submitted for histopathological examination comprised thin, flat membrane like piece of greyish white soft tissue measuring 1·4×1·2 cm. In thickness it varied from 1 to 1·5 mm. Both the surfaces were smooth and mucosa-like.

Microscopic description. Paraffin embedded sections stained with haematoxylin and eosin revealed vascularised bands of moderately dense fibrous connective tissue covered over by stratified squamous epithelium on both sides. Subepithelial tissue contained a few scattered, small groups of mononuclear cells (Fig. 3).

Discussion

The first clinical case of epitarsus was reported in 1895[4] and the condition fully described in 1899.[5] Herbert[6] used the term conjunctival bridge to denote the same condition.

The deformity is almost invariably seen in the upper lid, though its bilateral occurrence in the lower lids has also been reported.[1] In the present case membrane extended vertically from the upper to the lower fornix, bridging the eyeball on the temporal side. It was attached laterally to the lateral fornix, but the medial border was free, and a probe could be passed under it. Histopathological examination following resection of the fold showed moderately dense fibrovascular connective tissue covered by stratified squamous epithelium on both the sides (Fig. 3) as also reported by other workers.[1 3]

Many workers have documented the association of epitarsus with untreated or ill treated acute conjunctivitis in infants and children.[3 4] Adhesions of the amniotic bands to the epithelial covering of the eyeball and persistence of hypertrophic plica semilunaris have also been blamed for the occurrence of epitarsus.[1] On the other hand Schapringer[5] considered it to be a primary congenital deformity of the conjunctiva owing to the absence of inflammatory signs in many cases. The present case also did not have any clinical or histopathological signs of inflammation. The presence of a few mononuclear cells in the subepithelial tissue does not denote inflammation, for these may be present in case of congenital anomaly, as is not unusual with other congenital abnormalities.

From our observation and reports in the available literature we suggest classifying epitarsus aetiologically into two types: primary epitarsus, occurring purely as a congenital anomaly; and secondary epitarsus, following neglected cases of conjunctivitis. Singh and Grover[3] have described four clinical varieties of epitarsus depending on the extent of the deformity, namely intrafornix, fornix-tarsal, fornix-limbal, and interfornix. The lesion in the patient described here was clinically consistent with the interfornix type.

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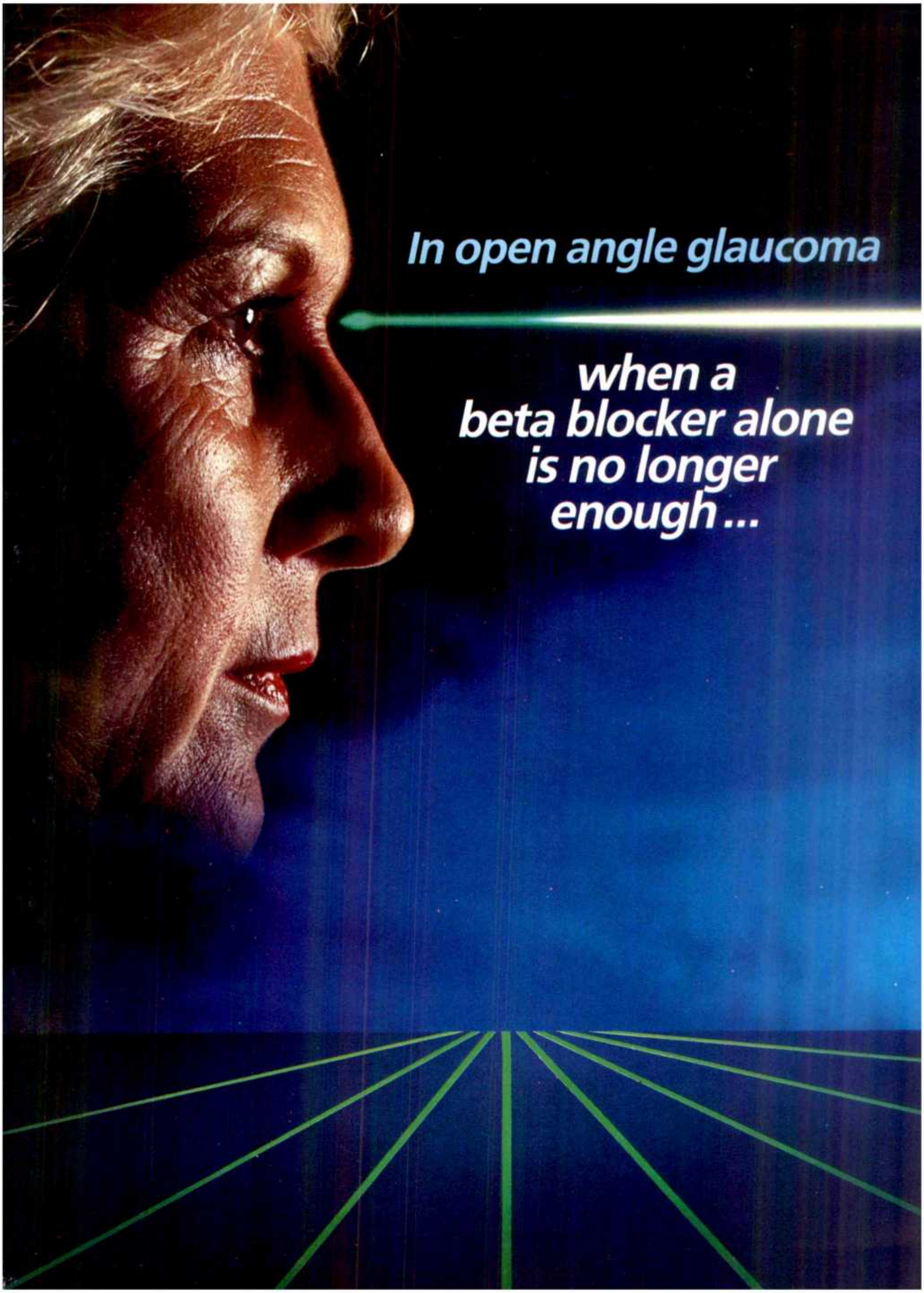
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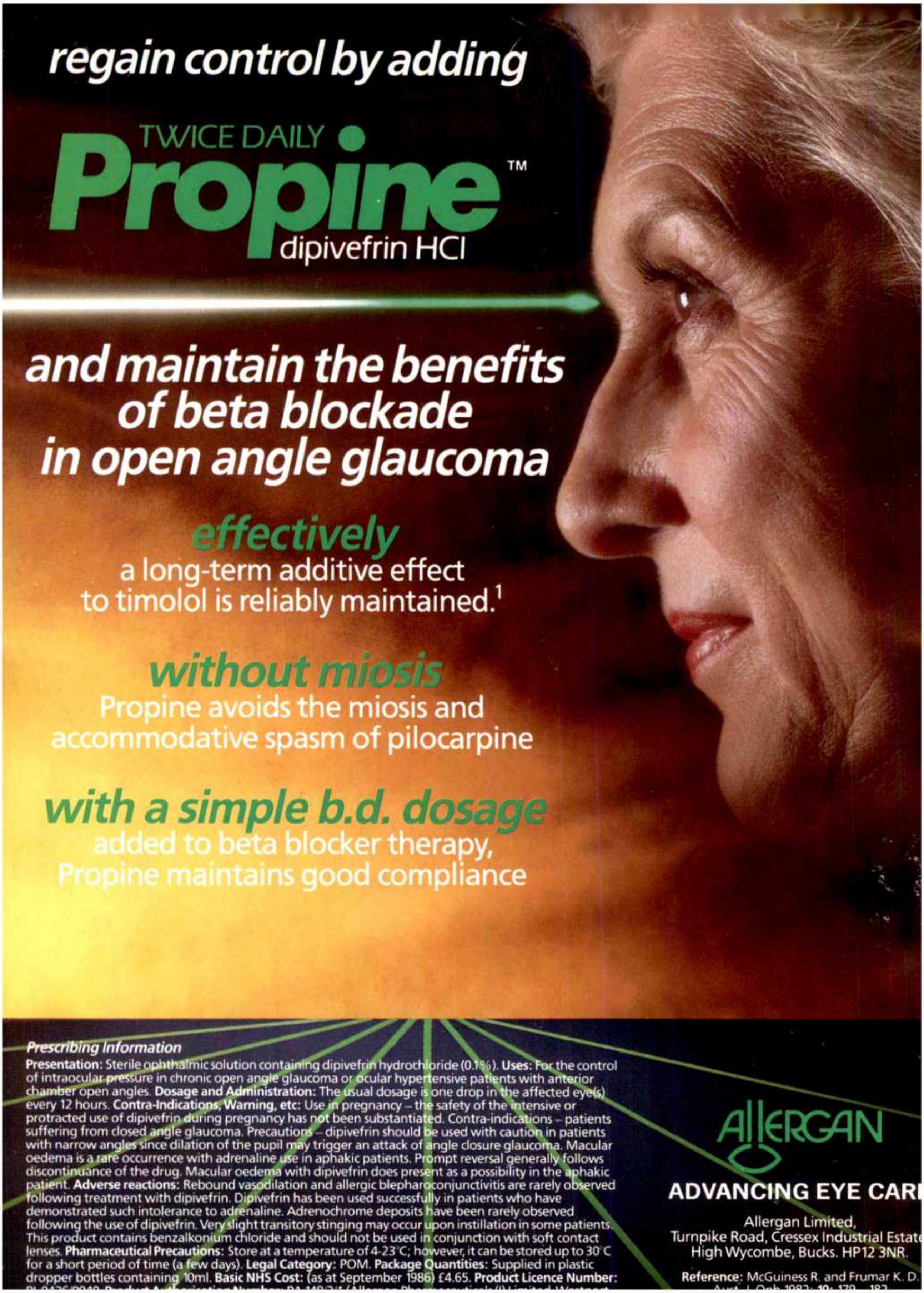

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Are their spectacles really necessary?

SIR, This editorial,[1] which is overtly critical of opticians, unjustifiably so in my view, has been brought to my attention. Although I am writing in my private capacity as an experienced ophthalmic optician, I am also the Scottish representative of the British College of Ophthalmic Opticians and chairman of the National Optical Consultative Committee.

The main defect in your editorial lies in the assumption that '80–90% of the prescriptions' for the 516 wearers of supposedly unnecessary spectacles out of 13 800 school children aged 10 years or less 'have been issued by non-medically qualified persons.' You give no source for that figure of 80–90% but it presumably applies to all age groups in the population.

But the 'School Eye Service' is staffed almost entirely by medically qualified ophthalmic practitioners who very probably account for a much higher proportion than 20 to 10% of refractions in the age group 10 years or under.

I have no access to figures in the Bristol area where Dr Stewart-Brown's survey was done,[2] but I personally have ascertained information about all spectacle dispensing in the Lothian, Scotland, area in February 1985. That month was chosen because it was probably an average month and because after 1 April 1985 these figures will not be available. Of the 85 children under the age of 10 years who had spectacles dispensed 37 were seen by an ophthalmic optician and 48 by a medically qualified ophthalmologist. I suspect the same would be true of the Bristol area, in which case a high proportion of the unnecessary spectacles, if indeed they were unnecessary, were prescribed by ophthalmologists.

Both Dr Stewart-Brown's paper, and indeed your own editorial, admit that hypermetropia requiring spectacles can well exist in the presence of normal visual acuity, yet these cases may constitute a significant proportion of those who received unnecessary spectacles.

Your editorial directs attention to a possible tendency for spectacles to be prescribed for headaches. The belief is widespread among ophthalmologists as well as general medical practitioners that even minor refractive errors are a cause of headaches which can be cured by spectacles.

Dr Stewart-Brown admits (p 879) that a proportion of children who appear to have normal visual acuity may have been inadequately tested by a series of medical officers with variable training (i.e., non-specialists, presumably).

You are critical of a 'non-medically qualified person' converting 'what begins as a simple task, a refraction,' into a 'pseudo-medical event.' In rebuttal I would claim that the main contributor to the early diagnosis of glaucoma as well as cataract and other diseases (mainly ophthalmic but some general) in this country is the ophthalmic optician.

30 Elder Street, Edinburgh JACK BROWN

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**The figure for '80–90% of the prescriptions' being issued by opticians was an estimate based on information issued by the Federation of Optical Corporate Bodies, 22 Nottingham Place, London W1, 'Optics at a Glance' 1984. This document states that 86·7% in 1983 were carried out by opticians and 67% of these tests resulted in a prescription for spectacles. Mr Brown appears to think that Dr Stewart-Brown's survey refers only to the Bristol area. However, if he consults the original paper again he will see that the children studied were all those born in the United Kingdom (excluding Northern Ireland) in the one week 7–11 April 1970.—Editor, *BJO*.

Transient monocular obscuration–amaurosis fugax?

SIR, I was very much interested in the paper 'Transient monocular obscuration–? amaurosis fugax: a case report' by Kosmorsky, Rosenfeld, and Burdel.[1] This was the case of a 73-year-old hypertensive man five years after right cataract extraction with iris fixation lens implant intermittently treated with pilocarpine to stabilise the lens. He presented repeated visual blurring the cause of which was found to be bleeding from abnormal superior angle vessels.

In 1972 we published the case of a 58-year-old hypertensive woman[2] who presented spontaneous hyphaema after topical administration of phenylephrine 10% for routine funduscopy followed by repeated pilocarpine 2% in order to speed the reconstriction of the pupils. A blood clot was suspended at 12 o'clock of the pupillary border, but we could not observe any abnormal vessel in the area. We believed that perhaps a previously present abnormal vessel was pressed upon by the fibres of the pupillary sphincter in rapid contraction caused by pilocarpine and then ruptured, causing the bleeding; however, no evidence of the ruptured vessel could be found afterwards. Fechner[3] described a case of spontaneous hyphaema with a ruptured microaneurysm at the pupillary margin and quoted a similar case described in 1932 by Tyson which was accompanied by vascular abnormality in one occipital lobe. Our patient,[2] who presented in 1976, has not had a recurrence of spontaneous hyphaema since then.

I am wondering if on the background of fragile new formed vessels near the iridectomy in the patient described by Kosmorsky *et al.* the intermittent administration of pilocarpine did not also play a role (perhaps by iris 'gymnastics' or by some pharmacological properties) in the appearance of hyphaema.

The differential diagnosis from carotid insufficiency was suggested by us in 1975 in a case of a 47-year-old woman[4] with anomalous iris vessels in the right eye, right orbit cavernous haemangioma, and a seven-year period of repeated attacks of intermittent blurring of vision due to spontaneous hyphaema. After the excision of the orbital haemiangioma in 1973 there have been no more attacks of spontaneous hyphaema up to the present.

Owing to the rarity of cases of spontaneous hyphaema I believe the article published in your journal this year to be important; it serves as a warning of the less known aetiological possibilities of intermittent blurring of vision. Moreover the symptom of erythropsia seems to me very important and contributory to the correct diagnosis.

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SIR, Any response to the query by Dr Manor about the possible association of pilocarpine usage and the occurrence of hyphaema in a group of such patients must be purely conjectural. Pilocarpine increases permeability and increases vasodilatation of iris vessels,[1 2] at least in experimental animals. If the new vessels in these patients were really fragile, one might suppose that there could be increased diapedesis of red blood cells and thus hyphaema, but the intermittency bespeaks a purely pharmacological effect. If pilocarpine is to be indicted, it would be more logical to suggest a mechanical stretching of vessels secondary to the effect of pilocarpine on the pupillary sphincter. On the other hand spontaneous bleeding from 'aneurysms of the iris' has been reported in a patient without any past surgical disorder.[3]

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Spectacle prescribing among 10-year-old children

SIR, We enjoyed Stewart-Brown's recent article[1] and the associated editorial[2] on spectacle lens prescribing among 10-year-old children. We note the suggestion that spectacles may have been unnecessarily supplied to many children whose unaided visual acuity was apparently normal. Clearly any evidence for substantial overprescribing in any branch of the National Health Service deserves investigation, though Stewart-Brown rightly recognises the difficulty of assessing the extent of children's refractive problems on the basis of visual acuity measurements alone, particularly when these are made by a variety of personnel under necessarily ill-controlled conditions of measurement. It is of interest to note that this type of controversy is not new, since Donders[3] was, over a century ago, already discussing the desirability of prescribing spectacles for hypermetropes with asthenopic symptoms.

It seems to us, however, that other important issues besides possible overprescribing arise from the data presented by Stewart-Brown. Her Tables 1 and 3 show that, for example, at least 10% of those children with 'bilateral marked distant defect' (i.e., both monocular Snellen acuities worse than 6/24), 80% of those with 'bilateral near defect' (worse than 9 on the Sheridan Gardner test), and 7% of those with 'bilateral marked mixed defect' (worse than 6/24 in each eye at distance and worse than 9 in one eye at near) were unprovided with spectacles. These figures correspond to a total of about 200 children who, in a group that had probably received rather more regular and careful medical examinations than the bulk of their peers, still had possible marked deficiencies in vision without apparently having received refractive assistance. Although the acknowledged limitations of the data do not allow us to assert that the visual abilities of these children would necessarily have been usefully improved by spectacles, it seems reasonable to suggest that children whose visual needs remain unsatisfied may represent at least as disturbing a problem as the approximately equal number whose acuities appear normal and yet have received spectacles.

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SIR, Drs Charman and Jennings make an important point about the 1970 birth cohort data, presented in my paper on spectacle prescribing. There were indeed a group of children who would appear by available criteria to warrant spectacles who had not been prescribed them, and the discussion did not focus on these children.

They raise a question mark about two quite different groups of children. Those with a distant visual acuity of ≤6/24 in both eyes (categories 4 and 10) and those with a near acuity of ≤9 in both eyes with perfect distant vision (category 5).

In the first group there were between 19 and 22 children without spectacles. For some of these children there were legitimate reasons for this lack of spectacles. For example, there were children with optic atrophy, macular degeneration, retinochoroiditis, and bilateral retinoblastoma who would not be expected to derive much benefit from spectacles; there were also ESN(S) children and severely emotionally disturbed children, for whom there may have been valid non-optical reasons for withholding spectacles. A detailed analysis of reasons for lack of spectacle prescription among all children in this group had not been undertaken when the paper was published, and I felt therefore it would be inappropriate to make a comment about this group. Some of these data have now been analysed and will be submitted for publication in a further paper.

The second group of children whom Drs Charman and Jennings comment upon are those with isolated near vision defects; only a small proportion of all the children in this group had been prescribed spectacles. I was not surprised to find a low prescription rate in this group, since screening for defective near vision is not common in schools,[1] and such children would therefore rarely be identified. This group was, however, the only one among children with defective vision in which an associated educational disadvantage that might be attributable to their untreated hypermetropia was detectable.[2] It is therefore a group which is worthy of comment and, indeed, further investigation.

Hypermetropia is very common in primary school children. It may be that these children would all benefit from spectacles, but it is important, before embarking upon such treatment policy, that a controlled trial be undertaken to establish exactly how spectacles could be of benefit. Such a study is currently being planned in the Department of Child Health Bristol and the Department of Ophthalmic Optics UWIST Cardiff.

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Screening for visual defects in preschool children

SIR, As part of the general ophthalmic service in Ayrshire and Arran Health Board primary orthoptic screening has been offered to all children at the age of 3½ since January 1978. A preliminary report of this has been published.[1] The methods used are often similar to those described by Ingram *et al.*,[2] but are always non-invasive and differ from those used by Ingram *et al.* in other ways. For example, the Sheridan Gardiner test (seven letters) is used for testing visual acuity, and the Frisby test is used for testing stereo acuity. Both those tests can give very accurate results and are eminently suitable for mass screening. Virtually no defects are missed and the false positive rate is approximately 1·5%. Unlike Ingram *et al.*, we consider an acceptable visual acuity to have to be at least 6/6.

We are now in the process of assessing the first five years of screening for both clinical effectiveness and cost effectiveness.

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SIR, I did know about the Camerons' paper in 1978, but overlooked reference to it, for which I apologise. I will await with interest publication of both their results of treating defective vision identified at 3½ and their methods of assessing 'cost effectiveness.' I still believe that a nationwide introduction of vision screening at 3½ should depend primarily on somebody being able to demonstrate that defective vision is more effectively treated if identified at 3½ than if it is left untreated until age 5+ (as at present).

I agree that the cost of any vision screening programme should also be considered, because we can no longer introduce a good idea just because it might be a 'good idea.'

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Atracurium and intraocular pressure

SIR, Murphy *et al's* paper on intraocular pressure (IOP) has just come to hand.[1] Their claim that the effect of atracurium had 'not hitherto been documented' is incorrect, as my coworkers and I studied and published[2] the effects of atracurium on IOP in 1984. It was nevertheless pleasing to see the results of our study independently corroborated.

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SIR, At the time of submission of our manuscript for publication there were no published reports on the effects of atracurium on intraocular pressure (IOP). Since that time two studies have been published apart from ours, that of Dr Maharaj *et al.*[1] and one by Tattersall, Manus, and Jackson.[2]

All three studies confirm the acceptability of atracurium for ophthalmic surgery.

In terms of purity of pharmacodynamic study, Dr Maharaj and colleagues' work is the most commendable. However, in the light of our study we feel that a more important fact should not be overlooked. The patient for whom changes in intraocular pressure are of most importance is the patient who has suffered a perforating eye injury. In this patient any change in IOP may cause further extrusion of intraocular contents and may critically jeopardise the eye. Our study, and that of Tattersall, Manus, and Jackson showed that, while atracurium is an acceptable drug for use in ophthalmic surgery, the considerable rise in IOP which results from laryngoscopy and tracheal intubation is of much greater significance. Until such time as we have an anaesthetic technique which is both rapid and unaccompanied by autonomic nervous overactivity, the perforated eye will remain a danger. Until this time, minor differences such as those demonstrated between atracurium, pancuronium, and fazadinium pale into insignificance.

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Obituary

A G Palin, BM, BCL, FRCS, FRCSEd

Mr A G Palin, formerly consultant ophthalmologist at the Bristol Eye Hospital, died on 26 January 1986 after a long illness patiently borne.

Anthony Palin graduated from Oxford and St Thomas's Hospital Medical School in 1934. He was appointed consultant ophthalmologist at Bristol in 1937 and served in the Royal Air Force during the war. On his return to Bristol until his retirement in 1972 he played a major part in establishing the Eye Hospital as one of the best units outside London. For many of these years he was senior surgeon in the days when this position carried the onerous duties of being chairman, head of the university department, and representative on many committees. Tony had no difficulty in carrying out these functions with aplomb, at the same time maintaining his reputation as a first class clinician. One mark of this distinction was the conferring of an honorary fellowship by the Royal College of Surgeons of England in 1970. There are many younger ophthalmologists, both in the UK and in Australia, who will remember his warm friendship and wise teaching.

Tony is survived by his wife Bobby, and two sons. NLD

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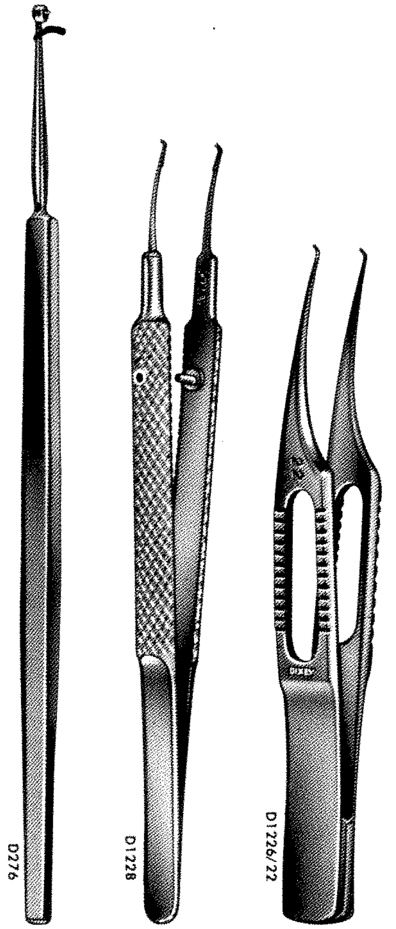

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